Automated Impedance Cardiography for Detecting Ischemic Left Ventricular Dysfunction during Exercise Testing

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Key Words
Impedance cardiography · Electrical bioimpedance · Hemodynamic monitoring · Exercise testing

Abstract
Automated impedance cardiography (ICG) is an attractive method for noninvasive hemodynamic evaluation. The objective of our study was to evaluate the feasibility and diagnostic value automated ICG in patients with suspected coronary artery disease (CAD). We measured stroke index (SI) and cardiac index (CI) in 65 patients with suspected CAD at rest and during bicycle exercise testing. All patients underwent subsequent cardiac catheterization including coronary angiography (CA). Depending on the results of CA, patients were divided into three groups, patients without significant CAD (group 0), single vessel disease (group 1) or multivessel disease (group 2–3). In a subset of 20 patients, automated ICG was compared to measurements of CI by the thermodilution (TD) method. Results: There were no significant differences in SI and CI at baseline between the three groups. At 75- and 100-watt exercise, patients in group 2–3 showed significantly lower mean values of SI and CI as compared to patients of group 0 and group 1 (all \( p < 0.05 \)), indicating exercise-induced ischaemic left ventricular (LV) dysfunction. Three patients had to be excluded because of inappropriate quality of the ICG signals during exercise. Comparison of automated ICG with TD measurements of CI showed good correlations between both methods at rest (\( r = 0.73 \)) and during exercise (\( r = 0.89–0.91 \)). Conclusions: We conclude that hemodynamic monitoring by automated ICG is both feasible and practical during exercise testing. Automated ICG can provide reliable and valuable additional diagnostic information on LV function during exercise which is helpful for selecting those patients for angiography who are likely to benefit from coronary interventions.

Introduction
In patients with suspected or proven coronary artery disease (CAD), stress testing by bicycle or treadmill exercise is an established method for evaluation of the individual exercise capacity and/or of the ischemic threshold. However, when critically reviewed, the diagnostic value of exercise ECG testing for detecting CAD is rather limited. The largest meta-analysis on the diagnostic value of exercise ECG testing for detecting CAD included over 24,000 patients from 147 studies and reported only a mean sensitivity of 68% and mean specificity of 77% [1]. These results actually mean that many patients would be
No significant CAD 20
Single-vessel disease 19
LAD stenosis 7
RCX stenosis 4
RCA stenosis 8
Two-vessel disease 12
Three-vessel disease 14

MI = Myocardial infarction; CABG = coronary artery bypass grafting; PTCA = percutaneous transluminal coronary angioplasty; CAD = coronary artery disease; LAD = left anterior descending; RCA = right coronary artery; RCX = Ramus circumflexus.

unecessarily referred for angiography if one would rely only on the result of exercise ECG testing. Therefore, especially in patients with chronic kidney disease who are likely to experience undesired side effects from angiography such as impairment of renal function caused by the contrast agent used during the procedure, a more accurate and predictive noninvasive testing is highly desirable. Moreover, exercise ECG testing does not provide any information on left ventricular function during exercise and its potential impairment by stress-induced ischemia. If additional hemodynamic information is required, the thermodilution (TD) method or the indicator (dye)-dilution method (Fick method) are the most widely used standard methods for hemodynamic monitoring. Invasive hemodynamic studies using right heart catheterization can, however, not be widely applied for diagnostic purposes since they require the appropriate technical equipment, are time-consuming, costly and – due to their invasive nature – not free of inherent up to lethal complications [2].

The validity of noninvasive hemodynamic measurements by impedance cardiography (ICG) has been recently reviewed by several authors [3–5]. The authors concluded that automated ICG can be viewed as a reliable and accurate method which can be used in many different clinical situations in which hemodynamic monitoring is needed. While ICG has been extensively studied and validated in healthy individuals and in the intensive care unit setting, only few studies with small sample sizes have examined and evaluated the diagnostic value of ICG in during exercise in either patients with suspected or manifest CAD [6–9].

The primary objective of our study was therefore to evaluate the feasibility and incremental diagnostic value of hemodynamic monitoring by automated ICG during bicycle exercise in patients with suspected or proven CAD. A secondary objective was to validate the hemodynamic measurements obtained by automated ICG versus the thermodilution (TD) method and to compare both methods.

Patients and Methods

Patients and Study Protocol

We serially examined 65 patients with suspected CAD who were referred for coronary angiography by conventional bicycle exercise testing. All patients received simultaneous hemodynamic monitoring by automated ICG during the exercise tests. The indication for coronary angiography was based either on suspected CAD because of typical angina symptoms, a known history of manifest CAD (previous myocardial infarction, CABG or PTCA) or atypical symptoms together with dyspnea on exertion and/or risk factors for CAD. All patients underwent cardiac catheterization within 1–5 days after the exercise test. The baseline characteristics of all study patients are given in Table 1.

In a subset of 20 patients in addition to coronary angiography, right heart catheterization was performed together with exercise testing for further evaluation of dyspnea and cardiac performance. In this substudy, simultaneous hemodynamic measurements by the TD method and automated ICG were performed at rest and during exercise to compare the results of both methods.

All ICG-derived hemodynamic data were evaluated after completion of the invasive studies by coronary angiography or right heart catheterization by investigators blinded to the results of the two invasive methods. Informed consent for participation in the study was obtained from all patients. The study was approved by the appropriate institutional ethical review board.

Bicycle Exercise Testing

All patients underwent conventional bicycle exercise testing in a semi-supine position. Continuous 12-lead ECG monitoring was performed in all patients. Exercise testing was routinely started at 50 W with increasing 3-min stages of 25 W until the age-predicted heart rate (85% of 220 minus age) was achieved. Other criteria for the termination of the exercise test were the presence of angina pectoris, significant ST depression, dyspnea, significant arrhythmias, hypertension (systolic blood pressure ≥220 mm Hg, diastolic blood pressure ≥110 mm Hg), other cardiac or circulatory symptoms (palpitations) or peripheral exhaustion.
Automated Impedance Cardiography

Continuous hemodynamic monitoring during the bicycle exercise test was performed by an automated ICG system (cardioscreen professional; Medis GmbH, Ilmenau, Germany). The ICG system consisted of a conventional laptop computer with the ICG signal processing software and a transmitting unit connected to three ECG electrodes and four pairs of electrodes for recording the thoracic bio-impedance field (‘four-pair method’). Correct identification of the points B (opening of the aortic valve), P (maximum systolic flow) and X (closure of the aortic valve) on the ICG curves were automatically confirmed by marker channels. The modified Bernstein formula [10] was used for calculation of stroke index (SI) and derived thereof, cardiac index (CI). The software of the ICG system was programmed to average and calculate all measurements automatically for five consecutive beats at each prespecified time point at rest and during the different exercise stages (i.e. at rest, 50, 75 and 100 W). These specific time points were indicated on a separate marker channel of the system for the hemodynamic evaluations. The system permitted on-line visibility of the recorded ECG as well the ICG signals and the calculated hemodynamic variables on a standard monitor.

Coronary Angiography

Conventional coronary angiography (Judkin’s technique) was performed in all patients. Significant CAD was defined as ≥ 50% reduction in luminal diameter of at least one major coronary vessel or its main branches. Evaluation of all coronary angiograms was done visually by agreement of two experienced investigators blinded to the results of the exercise tests and not involved in the ICG-based hemodynamic studies. Depending on the results of coronary angiography, patients were subdivided into three groups: patients without significant CAD (group 0), patients with single vessel disease (group 1) and patients with multivessel disease (groups 2–3). The results of the coronary angiography are included in table 1.

Right Heart Catheterization

All patients underwent right heart catheterization by a pulmonary artery catheter (Baxter Inc., Irvine, Calif., USA) which was introduced via the antecubital vein and, after inflation of the balloon, positioned into a pulmonary artery. The correct position was confirmed by the typical pressure curves which where continuously registered during the procedure by radiographic control. TD measurements of CI were obtained by manual bolus injections of iced water (4–6°C) independently from the respiratory cycle into the right atrium and detection by the thermistor probe at the distal end in the pulmonary artery. The first of four consecutive measurements was routinely skipped to avoid incorrect measurements. The thermodilution curve confirming correct injection was visible on a control screen. All calculations to derive SV and CO from the thermodilution curve confirming correct injection was visible on a control screen. All calculations to derive SV and CO from the thermodilution measurements using the Bland-Altman method were compared to the measurements of SV and CI by ICG and the thermodilution method. The results of the ICG measurements were compared to the thermodilution measurements using the Bland-Altman method [11].

Results

Exercise Testing

Twenty-eight of 42 patients with a pathologic coronary angiogram had a pathologic exercise ECG test result (sensitivity 67%), 17 of 20 patients without significant CAD had a normal exercise ECG test result (specificity 85%). Only 15 of 65 patients were able to achieve the age-predicted target heart rate (23%). Sensitivity of exercise ECG testing for detecting single vessel disease was lower (50%) than for detecting multivessel disease (80%). The positive predictive value of the exercise ECG test for predicting significant CAD was 83%, the negative predictive value was 45%. The exercise performances of all 65 patients by study group are given in table 2.

Hemodynamic Findings by Automated ICG

Three patients had to be excluded from automated ICG analysis because of inappropriate quality of the recorded ICG curves. The ICG-derived calculations for mean values of SI and CI at baseline and at 100-watt exercise per patients group of the remaining 62 patients are given in table 3 and figures 1 and 2.

Baseline values did not significantly differ between the three study groups. Bicycle exercise resulted in a signifi-
cant increase of SI and CI in group 0 and group 1 (p < 0.01) but not in groups 2–3. The mean increase of SI from baseline to 100 W was 67.8 ± 17.9% for patients with no significant CAD (group 1), 35.8 ± 13.3% for patients with single vessel disease (group 1) and –11.6 ± 15.2% for patients with multivessel disease (groups 2–3). For CI, mean increases from baseline were 134.1 ± 19.7% in group 0, 91.7 ± 18.7% in group 1 and 32.6 ± 24.2% in groups 2–3, respectively.

Combination of Hemodynamic Results with Exercise Testing

To further assess the diagnostic value of hemodynamic measurements of SI and CI by automated ICG performed during conventional exercise testing both methods were combined. Since in group 0 vs. group 1 and groups 2–3 the percentage increase (Δ%) of SI from baseline to and exercise stage of 100 was 58 ± 17% in group 0 vs. 34 ± 13% in group 1 and only 4.8 ± 6.3% in groups 2–3 we decided to interpret a percentage increase of SI from baseline to 100 W of at least ≥50% as normal. Using this criterion (meaning an exercise ECG test was also interpreted as pathologic if the ECG was normal but SI measured by automated ICG did not increase by ≥50% at 100-watt exercise) sensitivity rose from 67 to 76% (4 more patients with significant CAD detected). Following the same principle for interpretation the exercise-induced increase of CI, an increase of CI of at least 125% at 100 W was chosen as the threshold of normal vs. pathologic (compare respective percentage increases of CI at each exercise stage in table 3). Using this criterion 5 more patients with a negative exercise test but a pathologic angiographic result were identified (sensitivity rose to 78%). Specificity of exercise ECG testing, however, could be only improved by approximately 5%, respectively (from 85 to 90%) by the combined use of both methods since only one ‘false-positive’ patient detected by a pathologic exercise ECG test result could be interpreted as normal when his hemodynamic results were considered.

Comparison of Automated ICG versus the Thermodilution Method

The results of the measurements of CI by either TD or automated ICG and the respective coefficient of correlation at rest (baseline) and at each exercise stage are given in table 4. There were no significant differences between both methods. However, there were consistently higher CI values calculated from ICG-derived measurements as compared to the TD method. There was a good correlation between both methods at rest and at all exercise stages with increasing correlation at each exercise stage (table 4). The comparison of both methods using the Bland-Altman method showed a total mean difference of 0.05 ± 0.6 l/min/m² at baseline and of 0.41 ± 0.7 l/min/m² at 100-watt exercise with higher values of CI calculated by automated ICG versus those calculated by the TD method.
Automated Impedance Cardiography for Hemodynamic Monitoring

**Discussion**

In the present study we used automated ICG for monitoring SI and CI in patients with suspected CAD at rest and during bicycle exercise testing. Compared to invasive standard techniques for hemodynamic monitoring (e.g. the thermodilution (TD) technique or the Fick method) which require an experienced investigator, hemodynamic monitoring using automated ICG offers several apparent advantages: automated ICG is a time- and cost-effective method which could be easily applied also by non-specialists in a routine setting. Most importantly, hemodynamic studies by automated ICG can be performed outside the catheterization laboratory without using any contrast agent as an absolutely risk- and pain-free procedure for the patient which make automated ICG a method ideally suited for repeated or serial measurements at follow-up visits.

The present study is the first in which patients with suspected CAD have been investigated by automated ICG with the objective to improve the sensitivity and specificity of noninvasive testing by additional hemodynamic monitoring of LV function during exercise. Importantly and in contrast to previous studies, all patients in our study underwent subsequent coronary angiography so that all ICG-derived hemodynamic results could be linked to the patient’s coronary status.

Our study reports three major findings: Firstly, we demonstrated that hemodynamic monitoring by automated ICG is a feasible and reliable method not only at rest but also during bicycle exercise. By using automated ICG, we were able to increase sensitivity and specificity of conventional exercise ECG testing.

Secondly, by our ICG-based hemodynamic studies we were able to demonstrate the impairment of left ventricular performance during exercise not only in relation to the presence or absence of significant CAD, but also in relation to the number of affected vessels (one vessel disease, multivessel disease). While there were no significant differences at rest, there were significant differences in SI and CI at 100-watt exercise between patients with no angiographic evidence of significant CAD and those with single or multivessel disease (fig. 1, 2). Thirdly, the comparison of CI calculated by automated ICG with the respective values obtained by the TD method as a currently accepted and most widely used standard method for

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**Table 3.** Mean values of heart rate, stroke index and cardiac index at baseline and at 100-watt exercise

<table>
<thead>
<tr>
<th></th>
<th>Group 0 (n = 20)</th>
<th>Group 1 (n = 18)</th>
<th>Group 2/3 (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>baseline 100 W</td>
<td>baseline 100 W</td>
<td>baseline 100 W</td>
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<tr>
<td>HR, bpm</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>71.1 ± 10.2</td>
<td>71.5 ± 11.9</td>
<td>73.3 ± 13.4</td>
<td></td>
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<tr>
<td>112.9 ± 11.9*</td>
<td>114.5 ± 15.7*</td>
<td>116.7 ± 17.8*</td>
<td></td>
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<tr>
<td>SI, ml/m²</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>46.9 ± 6.2</td>
<td>47.7 ± 9.4</td>
<td>47.7 ± 10.5</td>
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<tr>
<td>74.4 ± 5.7*</td>
<td>64.2 ± 10.5*</td>
<td>50.0 ± 11.1*</td>
<td></td>
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<tr>
<td>CL, l/min/m²</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>3.4 ± 0.5</td>
<td>3.6 ± 0.6</td>
<td>3.6 ± 0.7</td>
<td></td>
</tr>
<tr>
<td>7.9 ± 0.8*</td>
<td>6.8 ± 1.1*</td>
<td>5.3 ± 1.1*</td>
<td></td>
</tr>
<tr>
<td>SI = Δ BL to 100 W, %</td>
<td>67.8 ± 17.9*</td>
<td>35.8 ± 13.3*</td>
<td></td>
</tr>
<tr>
<td>CI = Δ BL to 100 W, %</td>
<td>134.1 ± 19.8*</td>
<td>91.7 ± 18.7*</td>
<td></td>
</tr>
</tbody>
</table>

Significant differences of p ≤ 0.01 are indicated by *.

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**Table 4.** Comparison of cardiac index (CI) calculated by either the thermodilution (TD) method or automated impedance cardiography (ICG) at rest and at exercise stages of 50, 75 and 100 W

<table>
<thead>
<tr>
<th></th>
<th>TD</th>
<th>ICG</th>
<th>Δ ICG-TD</th>
<th>p value</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest, l/min/m²</td>
<td>3.15 ± 0.7</td>
<td>3.66 ± 0.8</td>
<td>0.52 ± 0.58</td>
<td>n.s.</td>
<td>0.73</td>
</tr>
<tr>
<td>50 W, l/min/m²</td>
<td>4.79 ± 1.1</td>
<td>5.42 ± 1.1</td>
<td>0.63 ± 0.52</td>
<td>n.s.</td>
<td>0.88</td>
</tr>
<tr>
<td>75 W, l/min/m²</td>
<td>5.58 ± 1.3</td>
<td>6.14 ± 1.2</td>
<td>0.56 ± 0.63</td>
<td>n.s.</td>
<td>0.87</td>
</tr>
<tr>
<td>100 W, l/min/m²</td>
<td>6.43 ± 1.4</td>
<td>6.84 ± 1.6</td>
<td>0.41 ± 0.67</td>
<td>n.s.</td>
<td>0.91</td>
</tr>
</tbody>
</table>

The last column gives the coefficient of correlation (r) between the two methods.
hemodynamic evaluation in a subset of 20 patients showed high correlations for measurements of CI at rest and during exercise (table 4).

**What Is the Additional Diagnostic Value of Automated ICG?**

The results of our study show that exercise-induced ischemic left-ventricular dysfunction can be detected by measurements of SI and CI by automated ICG. This posed the question what the additional diagnostic value of combining hemodynamic measurements by ICG with conventional exercise ECG testing would be. We did therefore combine the relative increase of the ICG-based hemodynamic findings for SI and CI at an exercise stage of 100 W (Δ BL to 100 W in expressed in %, compare table 3) with a normal or pathologic result of the exercise ECG test. Sensitivity for the detection of CAD was increased by 10%, while specificity was increased by 5%. Since sensitivity is the 'Achilles heel' of exercise ECG testing, we predict from the results of our study that the diagnostic value of exercise testing can be significantly increased by the combination of automated ICG with the results of conventional exercise ECG testing. Using such a combined approach to increase the accuracy of noninvasive testing would be of special value, i.e. in patients with known chronic kidney disease, in whom exposure to contrast agents should be avoided whenever possible and referral to angiography needs a careful risk-benefit assessment.

**Comparison with Previous ICG Studies Conducted during Exercise Testing**

However, although studied and validated under various clinical conditions, only four studies have been published which investigated automated ICG during exercise testing.

In one of the first studies comparing hemodynamic measurements obtained with an automated ICG system with invasive measurements (Fick method) not only at rest but also during exercise, 6 healthy males and 20 patients with suspected CAD underwent exercise testing and simultaneous measurements by both methods [6]. The authors reported no significant differences but highly significant correlations (r = 0.8–0.9) between both methods and a high reproducibility, reliability and accuracy of automated ICG versus the Fick method. However, unfortunately the authors did not describe the coronary status of their patients and did not investigate the potential of automated ICG to detect the impact and exercise-induced ischemia on hemodynamic variables in their patients.

In another study, 5 healthy volunteers were investigated at rest and during bicycle exercise by automated ICG and the Fick method [7]. The conclusion of this study for exercise measurements was that at least in healthy males automated ICG may systematically overestimate cardiac output. Automated ICG, the TD method and measurements obtained by the Fick method were compared in a study by Belardinelli et al. [8] in a series of 25 consecutive patients with documented CAD. Consistent with the results of our study, no significant differences between measurements of cardiac output between the three methods were found and the correlation of ICG versus TD and the Fick method were high (r = 0.9). Again, however, like in the study of Teo et al. [6], despite comparing the three methods, no efforts were made in this study to link the hemodynamic measurements to coronary status and assess their potential to diagnose exercise-induced ischemic left-ventricular dysfunction. In a more recent study, Tordi et al. [9] compared cardiac output measured by either automated ICG or the CO₂ rebreathing technique in competitive athletes during bicycle exercise up to heart rates of 160 beats/min. Consistent with the findings of our study, the correlation between both methods was again high (r = 0.82) and there were no significant differences between both methods. At higher heart rates, CO was overestimated by automated ICG as compared to the respective findings by the CO₂ rebreathing method, a finding which was however explained by increasing acidemia during exercise.

**Comparison with Previous Studies Comparing ICG versus the Thermodilution Method**

The diagnostic value and correlation of hemodynamic measurements of cardiac output (CO) or cardiac index (CI) calculated by automated ICG or the thermodilution method (TD) has been previously studied by several other groups [12–18]. These studies showed, consistently with the results of the present study, a good correlation between ICG-based hemodynamic measurements and the respective TD measurements with mean coefficient of correlation of approximately r = 0.8. The results of the respective studies and other comparative studies have been summarized in recent reviews [3–5] which all concluded that automated ICG is a valuable diagnostic method for hemodynamic measurements under various clinical conditions such as on the intensive care unit, before or after CABG or in acute trauma. The largest meta-analysis [3] including 27 studies reported a coefficient of correlation of r = 0.81 between ICG-derived hemodynamic measurements and the TD method. In non-ICU patients,
the coefficient of correlation between both methods was even higher ($r = 0.88$) [3].

The interesting and important finding of our substudy comparing ICG versus TD in this context is that we could confirm the previously reported good correlation between ICG and TD at rest also during exercise, a finding which is important when automated ICG should be potentially used for the diagnosis of ischemic left-ventricular dysfunction to detect CAD in the future. The correlation calculated in our substudy at exercise stages of 50, 75 and 100 W between both methods was between $r = 0.8$ and $r = 0.9$ (table 4), which is an excellent correlation for a rather small sample size of 20 patients.

Like in our study, ICG-based calculations of CI have however a tendency to overestimate CI in comparison with the TD method. Whereas previous studies describe discrepancies of up to $0.8–1.3 \text{l/min/m}^2$, the mean differences between both methods for measurements of CI were approximately $0.5 \text{l/min/m}^2$ with higher values obtained by automated ICG. Notably, this difference did also not increase during exercise. Due to comparable methodological problems with correct signal detection and related identification of correct measure points on first derivative of the thoracic bioimpedance curve, it is however not advisable to interpret ICG-derived measurements of ejection fraction [5, 19, 20].

**Other Clinical Applications of Automated ICG**

Despite its well-documented use for monitoring hemodynamics in clinical pharmacology studies, on the intensive care unit, in the operation theatre during cardiac surgery and in the emergency room [3–5], other future clinical applications of automated ICG will include monitoring of hemodynamics in patients with chronic heart failure [21–22] or pulmonary hypertension [23] for optimized titration of respective treatment regimens. With newly developed devices, even home-based telemetric monitoring of fluid status in patients with chronic heart failure and/or kidney disease is possible and currently under investigation.

**Study Limitations**

The results of the present study report data from a relatively small population. For a future characterization of a normal versus a pathologic response to exercise, data from a larger population than investigated in the present study will be required to define normal ranges for SI and CI during exercise testing. These ranges might also be different for exercise testing in a supine or upright position due to an either increased (supine position) or reduced preload (upright position on the treadmill). Applying other formula than the Bernstein formula for calculating SI or other electrode positions [24] than used in the present study might have also impacted the results of our study. However, comparing different methodological approaches for assessing hemodynamics was not the primary objective of the present study.

**Conclusions**

From the results of our study, we conclude that hemodynamic monitoring by automated ICG is a feasible and practicable method for hemodynamic monitoring during exercise testing. The combination of automated ICG and conventional bicycle exercise ECG testing results can provide reliable and valuable hemodynamic information which can increase the diagnostic value of noninvasive testing and helps to select those patients for angiography who are likely to benefit from coronary interventions.

**References**


