Cardisiography™, the novel approach to vector-cardiography analyzed with artificial intelligence: Scientific foundations, evidence, and future perspectives.

Cardiovascular diseases: A global health issue

In the 21st century, cardiovascular diseases (CVD) remain the leading cause of morbidity and mortality worldwide, when considering non-communicable diseases [1]. Unfortunately, the number of deaths due to cardiovascular diseases has risen by 12.5% globally over the past decade, accounting for approximately one in three global deaths [2, 3]. It comes as no surprise that ischemic heart disease (IHD) contributes the largest share to the global burden of CVD, and its prevalence as well as mortality increase dramatically with age [4].

The unexpected emergence of Coronavirus Disease (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), poses one of the greatest challenges to public health in history [5]. Since the first case of COVID-19 infection was reported in December 2019, the number of confirmed cases has reached around 668 million as of January 2023, resulting in 6.7 million deaths across 177 countries [6]. While several systems of the human body are affected by a COVID-19 infection, significant cardiovascular manifestations such as myocarditis, myocardial infarction (MI), arrhythmias, heart failure, Takotsubo cardiomyopathy, and post-COVID syndrome (chest pain, palpitations, reduced physical capacity) have been identified [5]. The underlying cardiovascular conditions, recent clinical manifestations, and the side effects of medications/vaccinations have come together to form a complex puzzle that clinicians have had to contend with [7].

Cardisiography – a Summary of Scientific Evidence

The following text provides an overview of the scientific evidence of Cardisiography (CSG), a non-invasive diagnostic tool for coronary heart disease. CSG is a 5-lead 3D vector cardiography with AI-based calculation, which examines 731 parameters to assess cardiovascular disease risk. CSG is an advancement of Cardiogoniometry (CGM)*, an adapted version of vectorcardiography first suggested in the 1920s [8–12].

In the past, numerous studies on the performance of CGM have been conducted [13–24]. The results of these studies, which proposed CGM as a new diagnostic tool for coronary heart disease, were summarized in a meta-analysis [22]. The pooled overall sensitivity was 71.7%, and the pooled specificity was 78.8%. According to Egger regression tests (P = 0.32), there was no bias in the studies.

Studies comparing CSG to other diagnostic methods show promising results. In a prospective study, CSG demonstrated high sensitivity (95.4%) and specificity (90%) in identifying relevant coronary stenoses [25]. Another study found CSG capable of diagnosing coronary artery disease with sensitivity (90-97%) and specificity (74-76%) [26]. These results were confirmed in a study using myocardial scintigraphy [27].

An exploratory study in a multicenter trial found that CSG reliably differentiated between high and low-risk groups for cardiovascular disease, potentially aiding in risk assessment. The CSG Index demonstrated a high negative predictive value (0.91) and outperformed classical risk factors in predicting cardiovascular risk. [28]

Additional abstracts have been accepted for the DGK Herbsttage, Bonn 2023 and American Heart Association Conference, November 2023.

**Please note that the Cardiogoniometry (CGM) technology belongs to Cardisio GmbH*

Basis of Cardisiography (Vector-Cardiography, Cardiogoniometry*)

Non-invasive diagnosis of coronary heart disease is still underdeveloped and improvable. To date, there is no simple and cost-effective method for reliable diagnosis. Apart from expensive and elaborate imaging procedures, exercise electrocardiography (stress ECG) is the most important available diagnostic method, albeit with only unsatisfactory sensitivity and specificity [31]. Cardisiography (CSG) is a 5-lead 3D vector cardiography with AI-based calculation (5L3DVCG-AI) of 731 parameters, which enables risk assessment of cardiovascular disease in primary care through an algorithm. CSG originates from the field of Cardiogoniometry (CGM), which in turn is an adapted version of vector cardiography, first described by Sanz et al. in 1983 [32].

For the detection of ischemic indications, the technology behind CGM focuses on recognizing abnormalities in the T-wave, which originate from the disturbed repolarization of cardiomyocytes due to cardiac pathology. The potentials from the five electrodes are described by 350 parameters, including angles, amplitudes, and velocities of the P, R, and T loops, among others. Parameters showing significant deviations can indicate impaired cellular repolarization and thus perfusion disorders [18]. This allows for the interpretation of electrical leads from only three linear projections, providing information that cannot be extracted from the usual 12-lead ECG [33].

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So, what are the differences and, more importantly, the advantages of CSG over CGM?

Fundamentally, CSG processes the electrical heart activity more comprehensively, delivering a higher level of information compared to CGM. Simultaneously, CSG employs not only more advanced CGM-specific parameters, such as energy density in the QRS and T complex, but also

introduces new parameters that consider the change in excitation speed of the electrical 3D signal. However, the most significant distinction between CGM and CSG is the integration of cloud-based AI framework for signal evaluation and identification of pathological signal structures in electrical heart activity, patented under EP3850640. CSG is an advancement of the vector-cardiography and CGM, already being routinely employed by a large number of practicing physicians, specialized clinics and hospitals both nationally and internationally.

As with CGM, studies have been and are being conducted for CSG. Substantial study results are available in which CSG was compared against various common examination methods.

CSG specific studies

In 2019, a total of 595 patients with clinical indications for catheterization were measured using CSG, and the diagnosis was confirmed through coronary angiography. The diagnosis was independently evaluated by two investigators. The study revealed that CSG could identify coronary artery disease (significant stenosis) at rest with a sensitivity of 90 ± 4% in females and 97 ± 3% in males. The specificity was 74 ± 10% (female) and 76 ± 9% (male). Hence, the overall diagnostic accuracy was 82 ± 6% (female) and 91 ± 3% (male) [26].

In 2020, Erkenov et al. conducted a prospective study involving 106 patients who underwent CSG measurements, following various exclusion criteria. All included patients had a clinical indication for coronary angiography, which was subsequently performed. The study demonstrated that CSG identified relevant stenoses with a sensitivity of 95.4% and a specificity of 90%. [25]

Apart from coronary angiography, CSG was also compared against myocardial scintigraphy. In 2022, a study with 88 consecutive patients showed a strong trend towards accuracy of 5L3DVCG-AI related to pathological MPS (Chi2: 3.2, p=0.07) with a sensitivity of 75% of 5L3DVCG-AI for a moderately or highly pathological MPS, a specificity of 58% and a negative predictive value (NPV) of 97%. In the subgroup of 62 patients with clinically suspected CVD, significant accuracy of 3D-VCG related to MPS was seen with a sensitivity 83%, specificity 66%, and NPV 98%. Thus, in a preselected study group of patients with clinically suspected, or known CVD, 5L3DVCG-AI has the potential to identify those patients not requiring interventional procedures as detected by MPS, with a significant NPV of 96%. [27]

In the most recent exploratory studies (presented at the poster sessions at the ESC 2023, Amsterdam, the DGK Herztage 2023, Bonn and the AHA 2023, Pennsylvania), we analyzed patients from a national, multicenter trial [28-30]. 407 Patients were analyzed from general cardiology practices and radiology center with patients referred for further diagnosis of suspected or confirmed CVD. Based on the CSG-Index, patients were either classified as high, medium, or low risk for CVD (medium + high defined as high CVD-risk). Confirmation of CVD was performed according to the practitioners' discretion blinded to the CSG-Index. The number of risk factors (mod. PROCAM score) were compared between the high- and low-risk group using an independent t-test. The number of cardiovascular risk factors was significantly higher in the high-risk CVD-group as defined by CSG-Index compared to low CVD-risk (4.0 [3.0

– 5.0] vs. 3.5 [2.0 – 4.0], $p < 0.05$). CSG-Index differentiated between suspected CVD with or without consequent PCI or CABG ($Chi2 = 4.02$, $p<0.05$). In conclusion, AI based 3D VCG is an innovative diagnostic tool that can help determine a patient's cardiovascular risk in resting condition for clinical and research purposes. CSG-Index reliably identified healthy controls (negative predictive value = 0.91) without signs or symptoms of CVD. The CSG-Index differentiated those with no signs and symptoms of CVD and patients with CVD and is a better predictor for cardiovascular risk than the classical risk factors. These results could be confirmed in a female subpopulation which is significant because women are often underdiagnosed with regards to CVD.

Furthermore, we could also compare the ECG time intervals in the conventional ECG with the 5L3DVCG-AI and could prove that the ECG intervals demonstrate a high correlation and low bias with the standard ECG.

Conclusion: CSG is superior to cardiovascular risk factor score in differentiating people at risk of CVD, especially in women. 5L3DVCG-AI offers the opportunity to identify people at risk for CVD in need of further cardiac diagnostics.
AI provides the opportunity for further improvement in this innovative diagnostic technology. 5L3DVCG-AI is an easy-to-use and inexpensive screening tool that has the potential to replace 12-lead ECG without major training or expertise.

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