VIA MEDICA

RESEARCH LETTER

Cardiology Journal
2024, Vol. 31, No. 3, 496–498
DOI: 10.5603/cj.96477

ISSN 1897–5593
eISSN 1898–018X

Dedicated devices for non-invasive cardiovascular risk assessment — the future of cardiovascular prevention

Bartosz Rolek, Ewelina Błażejowska, Grzegorz Procyk, Jakub Michał Zimodro, Aleksandra Gąsecka

1st Chair and Department of Cardiology, Medical University of Warsaw, Warsaw, Poland

Cardiovascular diseases (CVD) are the leading cause of death worldwide [1]. Early adequate diagnosis, lifestyle modification, and appropriate treatment may markedly decrease the mortality due to CVD.

Until now, endothelial function was assessed with the high-resolution brachial artery ultrasound – an operator-dependent method [2]. Recent technological developments have introduced objective, non-invasive devices measuring (i) skin fluorescence, (ii) pulse wave, (iii) and skin accumulation of advanced glycation end-products (AGEs). These devices provide valuable insights into individual CV risk, enabling early diagnosis and treatment.

Presented herein, is a concise overview of advantages, limitations, and possible clinical applications of the three currently available devices (Fig. 1).

Dysfunction of cutaneous microcirculation predisposes to atherosclerosis, thus should be considered in CV risk stratification. Assessment of cutaneous microcirculation is possible with flow mediated skin fluorescence (FMSF). FMSF measures changes in the nicotinamide adenine dinucleotide (NADH) fluorescence in the skin cells in response to post-occlusive reactive hyperemia, induced by blockage and release of blood flow on the forearm using an occlusion cuff. NADH accumulates in hypoxia or ischemia, while its oxidized form (NAD^+) occurs in hyperemia, leading to fluorescence alteration. Moreover, FMSF monitors myogenic microcirculatory oscillation, facilitating assessment of microcirculatory response to hypoxia. The risk of vascular complications is limited among people with reactive hyperemia response (RHR) >30%, hypoxia sensitivity (HS) > 30 and normoxia oscillatory index > 60%. The reproducibly of FMFS is excellent, with intra-patient variability less than 5% [3, 4].

FMSF enables early recognition of circulatory dysfunction and stratification of CV risk, leading to identification of individuals requiring medical attention. For instance, FMSF predicted vascular complications in the majority of patients with diabetes mellitus (DM) and hypertension, (RHR < 25%, HS < 30). Furthermore, FMSF evaluates mitochondrial function, thus might be used in monitoring metabolic diseases. Moreover, as FMSF measures NADH fluorescence in different physiological conditions, it might help assess the effects of physical activity on circulatory function [3, 4].

Nevertheless, FMSF has some limitations. Measurement of NADH fluorescence is performed on the forearm only. Thereby, no direct information is given regarding circulatory function in other body regions. Measurements are limited to the time of cuff occlusion and require the patient to remain still for several minutes. Moreover, the test must be executed in healthcare facilities due to high hardware requirements. However, a device using FMFS, AngioExpert (Angionica, Lodz, Poland), is already commercially available for healthcare providers, enabling its use in clinical practice.

Evaluation of endothelial function is also possible using the non-invasive, fast (15 min-

Address for correspondence: Aleksandra Gąsecka, MD, PhD, 1st Chair and Department of Cardiology, Medical University of Warsaw, Warsaw, Poland, e-mail: aleksandra.gasecka@wum.edu.pl

Received: 27.01.2023 Accepted: 23.12.2023 Early publication date: 14.05.2024

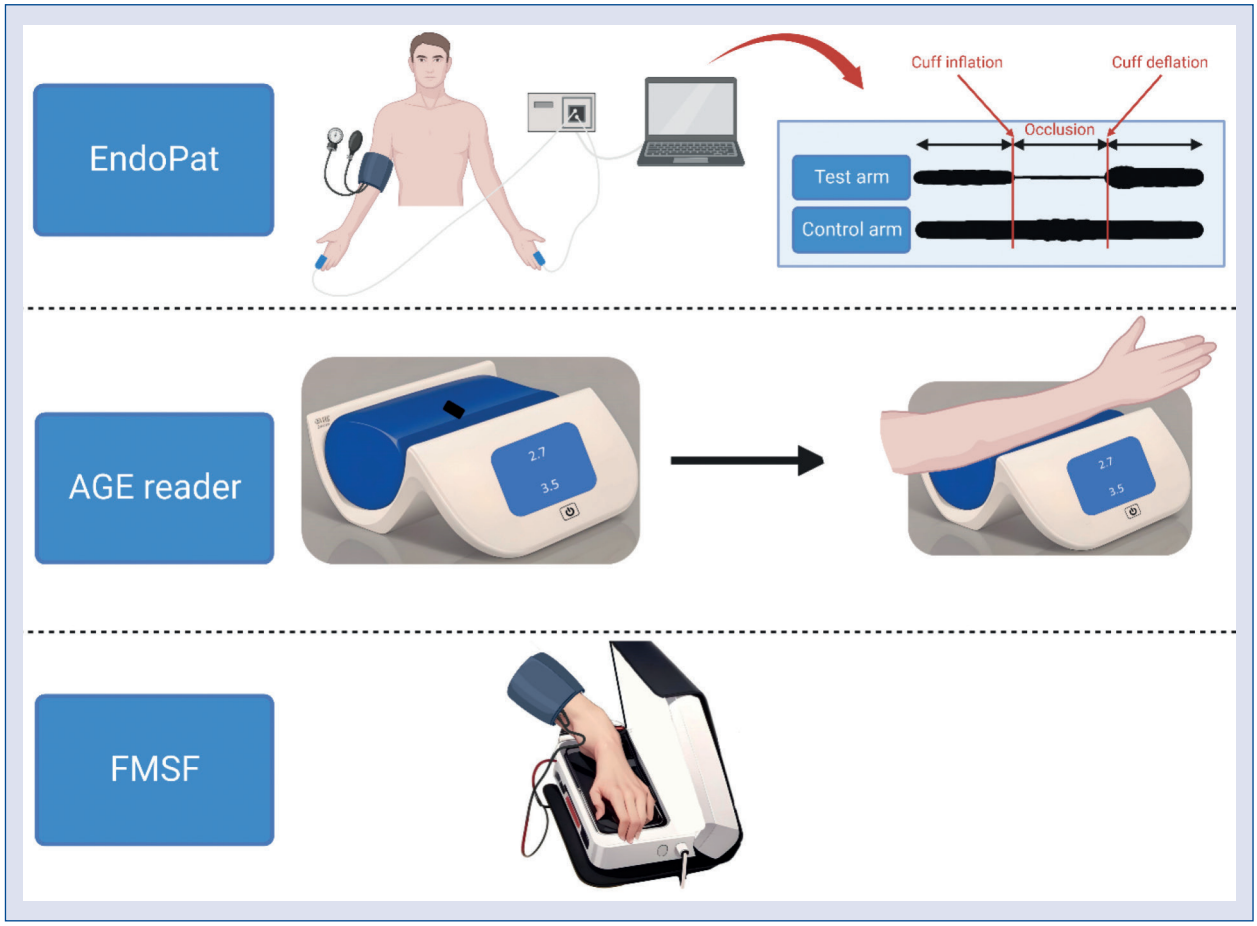

Figure 1. Working principles of use for EndoPat, AGE Reader, and flow mediated skin fluorescence (FMSF) devices.

utes), and non-operator-dependent EndoPat, which enables detection of endothelial dysfunction based on the registration of changes occurring in the digital pulse wave (peripheral arterial tone, PAT), measured using a pair of plethysmographic probes placed on the index fingers of each hand. Endothelial-mediated alterations in the PAT signal are induced by generating a downstream hyperemic response [2, 5].

EndoPat provides measurements for reactive hyperemia index (RHI) and arterial stiffness, known as augmentation index (AI). RHI values below 2 are categorized as endothelial dysfunction, with a mean intra-individual variability of 13%. AI correct values are between -30% and -10% with a mean intra-individual variability of 37%. EndoPat could be useful in recognizing patients at the earliest stage of CVD, showing vascular disfunction in patients with DM, familiar hypercholesterolemia, obesity, inflammatory bowel disease, Fontan survivors, and could monitor the effects of metformin and sulfonylurea treatment [2, 5].

Despite many advantages, availability of the equipment is limited. Moreover, whereas RHI is stable over time, AI showed variability, which limited its value. Moreover, EndoPat was not effective in detecting robust interventions, e.g., smoking cessation, which impact endothelial function [2, 5].

Another device enabling non-invasive CV risk assessment is AGE Reader. It uses the skin autofluorescence phenomenon due to AGEs that possess fluorescent properties. The results are expressed in arbitrary units (AU), and the intra-patient coefficient of variation is 5% [6, 7]. AGE Reader was initially used to assess DM. Nevertheless, correlations with other diseases were found, including CVD and renal diseases. For example, skin autofluorescence measured by AGE Reader predicted future CV events in DM patients better than cholesterol or blood pressure levels [8]. Patients with subclinical and clinical atherosclerosis had higher skin autofluorescence independent of atherosclerosis risk factors as assessed in the multivariate analysis (subclinical 2.11 AU; clinical 2.71 AU, controls 1.87 AU) [7].

AGE Reader offers significant advantages, notably its quick measurement time of 12 seconds. Furthermore, it has been used in clinical practice and research since 2006, with extensive validation. Beyond assessing CV risk, it serves as a mortality risk factor in DM, peripheral artery disease, and chronic kidney disease [7]. The measurement is patient-friendly thanks to the short time and non-invasiveness.

However, multiple factors may affect evaluation of skin autofluorescence, which is the main disadvantage of AGE Reader. These include diet, smoking status, physical activity, or renal function. Another limitation of this method is that skin autofluorescence can be measured reliably only in individuals with skin reflectance values > 6%.

AGE Reader may serve as an effective and easy adjunctive to other methods implemented for CV risk stratification, such as computed tomography angiography, ankle-brachial index, or carotid ultrasound. However, none of these methods are currently recommended for routine use as a screening tool and they mostly serve for risk reclassification in patients with intermediate CV risk. In the future, utilization of lab-on-chip nanotechnology [9] might enable detection of specific atherosclerotic-related biomarkers and facilitate identification of atherosclerosis-related CVD at an early preclinical stage. This approach will be explored in the "AtheroSClerosis alerT: detect the EARLY onset of multiple manifestations of atherosclerosis in a single assay" study, conducted by the authors.

In conclusion, the emergence of non-invasive devices for CV risk assessment represents advancement in preventing CVD. Such devices offer a promising alternative to invasive procedures, providing insights into individual CV health. By enabling early detection and risk stratification, non-invasive devices empower physicians to implement adequate interventions, such as lifestyle modification or pharmacotherapy, to reduce the risk of CV events.

Funding: None declared.

Conflict of interests: None declared.

List of abbreviations:

CVD — cardiovascular diseases
CV — cardiovascular
FMSF — flow mediated skin fluorescence
NADH — nicotinamide adenine dinucleotide
NAD+ — nicotinamide adenine dinucleotide oxidized form
PAT — peripheral arterial tone

References

1. Rana JS, Khan SS, Lloyd-Jones DM, et al. Changes in mortality in top 10 causes of death from 2011 to 2018. J Gen Intern Med. 2021; 36(8): 2517–2518, doi: 10.1007/s11606-020-06070-z, indexed in Pubmed: 32705476.
2. Moerland M, Kales AJ, Schrier L, et al. Evaluation of the EndoPAT as a tool to assess endothelial function. Int J Vasc Med. 2012; 2012: 904141, doi: 10.1155/2012/904141, indexed in Pubmed: 22500237.
3. Gebicki J, Katarzynska J, Marcinek A. effect of psychological stress on microcirculation oscillations: diagnostic aspects. Vasc Health Risk Manag. 2023; 19: 79–82, doi: 10.2147/VHRM.S399082, indexed in Pubmed: 36798618.
4. Marcinek A, Katarzynska J, Sieron L, et al. Non-invasive assessment of vascular circulation based on flow mediated skin fluorescence (FMSF). Biology (Basel). 2023; 12(3): 385, doi: 10.3390/biology12030385, indexed in Pubmed: 36979077.
5. Hayden J, O'Donnell G, deLaunois I, et al. Endothelial peripheral arterial tonometry (Endo-PAT 2000) use in paediatric patients: a systematic review. BMJ Open. 2023; 13(1): e062098, doi: 10.1136/bmjopen-2022-062098, indexed in Pubmed: 36657756.
6. Meerwaldt R, Graaff R, Oomen PHN, et al. Simple non-invasive assessment of advanced glycation endproduct accumulation. Diabetologia. 2004; 47(7): 1324–1330, doi: 10.1007/s00125-004-1451-2, indexed in Pubmed: 15243705.
7. den Dekker MAM, Zwiers M, van den Heuvel ER, et al. Skin autofluorescence, a non-invasive marker for AGE accumulation, is associated with the degree of atherosclerosis. PLoS One. 2013; 8(12): e83084, doi: 10.1371/journal.pone.0083084, indexed in Pubmed: 24376641.
8. Boersma HE, van Waateringe RP, van der Klauw MM, et al. Skin autofluorescence predicts new cardiovascular disease and mortality in people with type 2 diabetes. BMC Endocr Disord. 2021; 21(1): 14, doi: 10.1186/s12902-020-00676-4, indexed in Pubmed: 33435948.
9. Gorjikhah F, Davaran S, Salehi R, et al. Improving „lab-on-a-chip" techniques using biomedical nanotechnology: a review. Artif Cells Nanomed Biotechnol. 2016; 44(7): 1609–1614, doi: 10.3109/21691401.2015.1129619, indexed in Pubmed: 26758969.