

CAPILLAROSCOPY AND ENDOPAT – HELPFUL METHODS FOR THE EARLY ASSESSMENT OF INCREASED CARDIOVASCULAR RISK IN ANOREXIA NERVOSA?

FERENCOVA NIKOLA^{1*}, VISNOVCOVA ZUZANA¹, ONDREJKA IGOR²,
TONHAJZEROVA INGRID³

¹Biomedical Centre Martin, Jessenius Faculty of Medicine in Martin,
Comenius University in Bratislava, Martin, Slovak Republic

²Psychiatric Clinic, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava,
and University Hospital Martin, Martin, Slovak Republic

³Department of Physiology, Jessenius Faculty of Medicine in Martin,
Comenius University in Bratislava, Martin, Slovak Republic

A b s t r a c t

Anorexia nervosa (AN) as a life-threatening eating disorder is linked to a high mortality risk with many deaths attributable to cardiovascular etiology. Cardiovascular complications in AN include structural as well as functional cardiac alterations, hemodynamic changes, and peripheral vascular abnormalities. Despite the fact that peripheral vascular abnormalities are not identified as a major AN complication, several manifestations of peripheral vascular dysregulation including Raynaud's phenomenon and endothelial dysfunction have been described and, therefore, warrant attention. This article briefly summarizes so far findings of microvascular alterations in AN patients and presents easily accessible and non-invasive procedures for a microvascular evaluation such as capillaroscopy and endothelium-related peripheral arterial tone (EndoPAT) which could be involved in the clinical diagnostic process for the earliest identification of an increased risk of later cardiovascular complications.

Keywords: capillaroscopy, endothelial function, peripheral vascular abnormalities, cardiovascular risk, anorexia nervosa

INTRODUCTION

Anorexia nervosa (AN) represents a serious eating disorder commonly associated with other medical complications such as cardiovascular ones. Alterations in the cardiovascular system on the functional (e.g. bradycardia, prolongation of QT interval) and structural (e.g. reduction of left ventricular mass) levels can occur in approximately 75–85% of AN patients (1, 2). Among others commonly reported cardiovascular complications in AN, peripheral vascular abnormalities caused by dysregulation between peripheral vasoconstriction and vasodilatation mechanisms clinically appear with Raynaud's phenomenon (RP), a distinctive syndrome, characterized by episodic transient spasms of the peripheral vessels leading to digital ischemia associated with digits' discoloration that may be caused by the reflex vasoconstriction to emotional stress and low temperatures have been described (3–6). In this context, already Luck and Wakeling pointed to elevated cutaneous vaso-responsiveness to cold in anorexic patients (7). Although since then several studies evaluated the relationship between peripheral vascular alterations and AN (for review (5)), future research

Corresponding author: Nikola Ferencova, MD, PhD.; nikola.ferencova@uniba.sk

© 2023 Ferencova N. et al.

This work is licensed under the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 License
(<https://creativecommons.org/licenses/by-nc-nd/4.0/>)

is needed to reveal the precise AN-vascular health association. Moreover, endothelial dysfunction as a key factor in the development of atherosclerotic disease, predicting an increased rate of adverse cardiovascular events, has been described in anorexic patients (8). Therefore, routine monitoring of the cardiovascular health in AN patients should be considered to minimize a cardiovascular disease risk. In this aspect, the evaluation of microcirculation and endothelial function could offer an easy and non-invasive way for the earliest detection of peripheral vascular abnormalities in AN (9, 10).

NAILFOLD CAPILLAROSCOPY (NC)

NC is a non-invasive and easy-to-use imaging technique to evaluate microcirculation and capillary structure in the nailbed area. The main application of NC is the assessment of microvascular impairment in RP with a focus to differentiate between primary and secondary forms of RP (11, 12). The gold standard between capillaroscopic methods to perform nailfold capillaroscopy is the nailfold videocapillaroscopy (NVC) with a 200× magnification, capturing at least two adjacent fields of a linear millimeter (mm) in the middle of the finger (13). It has been shown that the sensitivity to reliably detect capillary abnormalities increases as more fingers were examined with the recommendation of eight-fingers evaluation, however, in the case of time pressure, the two-finger combination (both ring fingers) to detect capillary abnormalities may be used (14). NVC quantitative assessment involves capillaroscopic characteristics such as capillary density, capillary dimension, capillary morphology, and presence/absence of hemorrhages that are standardly evaluated per unit of quantity (i.e. per linear mm). Capillary density as the most reliable capillaroscopic parameter is used for the prediction of the disease progression and treatment monitoring. In NVC qualitative assessment – “scleroderma pattern” – further subgraded as early, active, or late is estimated (as reviewed in (13)). Based on the capillaroscopic characteristics – the image may refer to changes specific to the “scleroderma pattern” as occurring in scleroderma spectrum diseases, or the image is normal or has non-specific abnormalities as occurring in the healthy population, in primary RP or in connective tissue diseases other than systemic sclerosis (13). The normal capillaroscopic pattern is characterized by high skin transparency, absence of morphological abnormalities, uniformity of diameter and distribution of the capillaries, and hairpin capillaries arranged in a parallel fashion to each other. Early scleroderma pattern is defined as enlarged capillaries (diameter >20 µm and <50 µm), few (<4–6/mm) giant capillaries (diameter >50 µm), few microhemorrhages, fragmentation of the blood column with a granular appearance, and lack of capillary loss. Active scleroderma pattern represents more than six giant capillaries/mm, frequent capillary hemorrhages, 20–30% loss of capillaries, disorganization of the capillary architecture; and late scleroderma pattern is characterized by a 50–70% loss of capillaries with large avascular areas, disorganization of the normal capillary array, ramified/bushy capillaries, and neovascularization (9, 13, 15–18). The examination requires a proper preparation of the patient. The patient should have no history of trauma to the distal phalanges (including manicure), so the nail beds show no evidence of an infection and/or wound. The patient should not have artificial nails or nail polish. Moreover, the patient should be placed at least 15 minutes before the examination at a standard room temperature (22–25°C) to allow the nail fold capillary network to adapt (19).

It is important to note that there is an evidence of the association between nailfold capillaroscopic morphology and palmar digital arteries’ morphology and blood flow findings indicating that the microvascular damage and its progression is linked to macrovascular disease contributing to the increased risk of cardiovascular events (20). Moreover, the follow-up study has reported the association between RP and increased cardiovascular mortality indicating that RP can represent a precursor of undiagnosed vascular disease (21). Thus, present symptoms of microvascular abnormalities deserve attention in anorexic patients.

EVALUATION OF THE ENDOTHELIAL FUNCTION (EndoPAT)

Assessment of the flow-mediated arteries' vasodilation dependent on the proper endothelial function represents an entrenched measure of vascular health (22). Healthy endothelium as a monolayer of endothelial cells covering the vascular beds' lumen produces a wide range of factors as a response to various signals to regulate predominantly the vascular tone *via* the release of vasoactive molecules constricting or relaxing the vessels playing a key role in the maintaining the balance of oxygen supply to tissues and metabolic demand. Healthy endothelium also regulates the proliferation of smooth muscle cells or cellular adhesion (23, 24). Contrary, endothelial dysfunction is characterized by an imbalance between vasodilators and vasoconstrictors leading to an impairment of endothelium-dependent vasodilation, i.e. vessels' inability to adequately dilate in response to the stimulus. Moreover, endothelial dysfunction also comprises the activation of pro-inflammatory and pro-coagulatory *milieu*. Endothelial dysfunction thus represents a major contributor to atherosclerosis and a well-known predictor of an increased cardiovascular risk (25–27). Endothelial (dys)function can be assessed by numerous methods including the EndoPAT device which records the arterial pulse volume changes through the plethysmographic probes placed on the index fingers of each hand and transforms them to a peripheral arterial tone signal. A measure of endothelial function *via* changes in the vascular tone mediated by the endothelium is elicited by creating a hyperemic response after occlusion of the blood flow through the brachial artery with a cuff inflated to supra-systolic values for 5 minutes on the non-dominant hand followed by a consequent blood pressure cuff deflation. The recorded values are normalized to measures recorded from the contra-lateral arm used to control the concomitant non-endothelium dependent changes in peripheral arterial tone (e.g. fluctuations in the sympathetic nervous system activity) (25, 28–30). The obtained data are automatically analyzed by the system with the calculation of an endothelial function index (i.e. Reactive Hyperemia Index – RHI) defined as the ratio between average pre-occlusion baseline pulse wave amplitude and post-occlusion pulse wave amplitude measured during the one-minute period after 90 seconds of reactive hyperemia beginning, with RHI value less than 1.67 considered as abnormal (31). Limitations for the examination include digits' deformities which preclude adequate signal acquisition, medical conditions prohibiting blood flow occlusion in both arms, and the use of short-acting nitroglycerine (31).

PERIPHERAL VASCULAR ALTERATIONS IN ANOREXIA NERVOSA

Regarding the synergistic relationship of AN and RP on microvascular impairment, De Martinis et al. (9) revealed an early scleroderma pattern in 59% of patients suffering from both (AN+RP) and in 55% of RP patients with AN history. These findings outline the detection of capillaroscopic abnormalities in AN patients/individuals formerly suffering from AN with concomitant RP (9). Regarding AN and RP during adolescence, Kasap-Cuceoglu et al. revealed minor and major capillaroscopic changes including enlarged capillaries, mild tortuosity, microhemorrhages, capillary ramifications, capillary disorganization, and capillary loss in AN adolescents. Moreover, there were only minor capillaroscopic findings including mild capillary dilation and tortuosity in adolescents with RP (32). It is important to note that an association between capillaroscopic microvascular abnormalities and peripheral endothelial dysfunction was found (33, 34). In the view of endothelial dysfunction assessed by EndoPAT in anorexia nervosa, Suntharos et al. reported no significant differences in RHI between anorexic patients and the control group (10), while Springall et al. revealed a reduced endothelial function in young adult AN patients who formerly suffered from AN during adolescence (35). Moreover, Palova et al. reported a decreased vasodilatation in AN patients compared to the healthy subjects using the evaluation of flow-mediated dilatation of the brachial artery (8). Based on these above-mentioned findings, future research in the AN-microvascular health association and its contribution to cardiovascular complications is needed. Potential peripheral vascular abnormalities associated with AN are summarized in Figure 1.

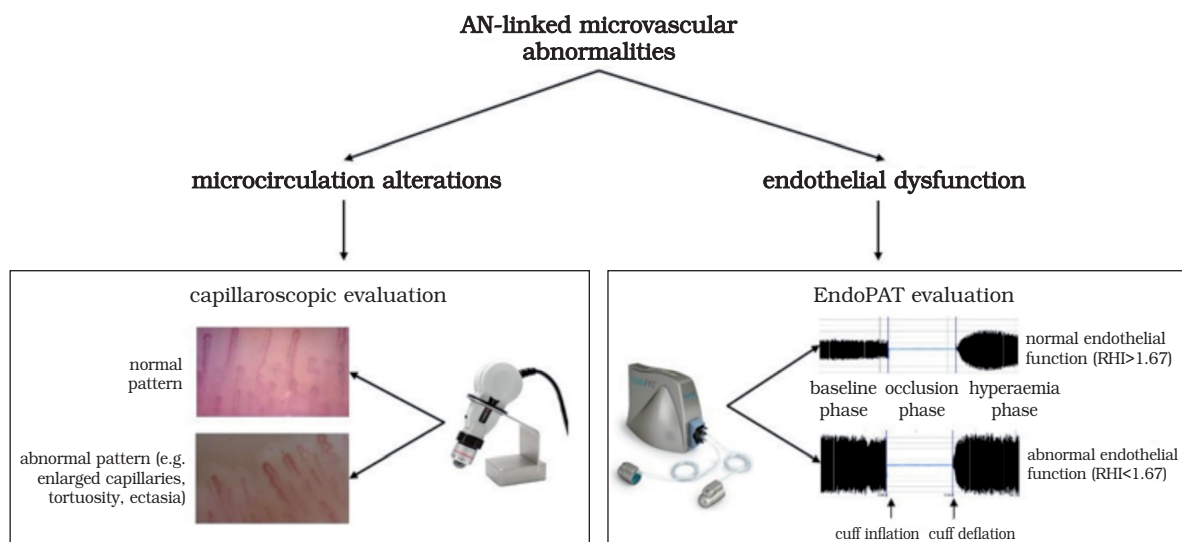


Fig.1. Evaluation of peripheral vascular abnormalities which can be associated with anorexia nervosa (AN). RHI – Reactive Hyperemia Index

CONCLUSION

The nailfold capillaroscopy and EndoPAT can be considered promising non-invasive methods for an early detection of AN-linked microvascular damage which, in combination with additional methods, may represent important diagnostic tools to detect the earliest peripheral vascular dysfunctions in anorexic patients. We believe that a detailed non-invasive assessment of AN-linked vascular abnormalities could contribute to a better understanding of pathophysiological mechanisms leading to a higher cardiovascular risk in anorexia nervosa, improving thus an early diagnosis, personalized prevention, and therapy of AN-linked cardiovascular complications.

Funding: This work was supported by Slovak Scientific Grant Agency under grant VEGA 1/0190/20.
Conflicts of Interest: The authors declare no conflict of interest.

REFERENCES

1. Milano W, Capasso A. Cardiovascular alterations in eating disorders. *Cardiovasc Disord Med*. 2018; 3 (2): 1-3.
2. Giovinazzo S, Sukkar SG, Rosa GM, Zappi A, Bezante GP, Balbi M, Brunelli C. Anorexia nervosa and heart disease: a systematic review. *Eat Weight Disord*. 2019; 24 (2): 199-207.
3. Yucel B, Uzun AK, Ozbey N, Kamali S, Yager J. Anorexia nervosa and Raynauds phenomenon: A case report. *Int J Eat Disord* 2007; 40 (8): 762-5.
4. Nawaz I, Nawaz Y, Nawaz E, Manan MR, Mahmood A. Raynaud's Phenomenon: Reviewing the Pathophysiology and Management Strategies. *Cureus* 2022; 14 (1): e21681.
5. Sirufo MM, Ginaldi L, De Martinis M. Peripheral vascular abnormalities in anorexia nervosa: A psycho-neuro-immune-metabolic connection. *Int J Mol Sci* 2021; 22 (9): 5043.
6. Sachs KV, Harnke B, Mehler PS, Krantz MJ. Cardiovascular complications of anorexia nervosa: A systematic review. *Int J Eat Disord* 2016; 49 (3): 238-48.
7. Luck P, Wakeling A. Increased cutaneous vasoreactivity to cold in anorexia nervosa. *Clin Sci (Lond)* 1981; 61 (5): 559-67.

8. Palova S, Charvat J, Chlumsky J. Flow-mediated vasodilatation in the patients with anorexia nervosa. *Bratisl Lek Listy* 2013; 114 (11): 634–6.
9. De Martinis M, Sirufo MM, Ginaldi L. Raynaud's phenomenon and nailfold capillaroscopic findings in anorexia nervosa. *Curr Med Res Opin* 2018; 34 (3): 547–50.
10. Suntharos P, Almeida Jones M, Seiden H, Fisher M, Gruber D, Rosen LM, Blaufox AD, Cooper RS. Endothelial function evaluation in patients with anorexia nervosa. *J Integr Cardiol* 2016; 2 (3): 287–91.
11. Ingegnoli F, Smith V, Sulli A, Cutolo M. Capillaroscopy in Routine Diagnostics: Potentials and Limitations. *Curr Rheumatol Rev* 2018; 14 (1): 5–11.
12. Ciaffi J, Ajasllari N, Mancarella L, Brusi V, Meliconi R, Ursini F. Nailfold capillaroscopy in common non-rheumatic conditions: A systematic review and applications for clinical practice. *Microvasc Res* 2020; 131: 104036.
13. Smith V, Herrick AL, Ingegnoli F, Damjanov N, De Angelis R, Denton CP, Distler O, Espejo K, Foeldvari I, Frech T, Garro B, Gutierrez M, Gyger G, Hachulla E, Hesselstrand R, Iagnocco A, Kayser C, Melsens K, Müller-Ladner U, Paolino S, Pizzorni C, Radic M, Riccieri V, Snow M, Stevens W, Sulli A, van Laar JM, Vonk MC, Vanhaecke A, Cutolo M. Standardisation of nailfold capillaroscopy for the assessment of patients with Raynaud's phenomenon and systemic sclerosis. *Autoimmun Rev* 2020; 19 (3): 102458.
14. Dinsdale G, Roberts C, Moore T, Manning J, Berks M, Allen J, Anderson ME, Cutolo M, Hesselstrand R, Howell K, Pizzorni C, Smith V, Sulli A, Wildt M, Taylor C, Murray A, Herrick AL. Nailfold capillaroscopy – How many fingers should be examined to detect abnormality? *Rheumatology (Oxford)* 2019; 58 (2): 284–8.
15. Wigley FM, Flavahan NA. Raynaud's Phenomenon. *N Engl J Med* 2016; 375 (6): 556–65.
16. Ingegnoli F, Ardoino I, Boracchi P, Cutolo M, EUSTAR co-authors. Nailfold capillaroscopy in systemic sclerosis: Data from the EULAR scleroderma trials and research (EUSTAR) database. *Microvasc Res* 2013; 89: 122–8.
17. Cutolo M, Melsens K, Herrick AL, Foeldvari I, Deschepper E, De Keyser F, Distler O, Ingegnoli F, Mostmans Y, Müller-Ladner U, Pizzorni C, Riccieri V, Ruaro B, Sulli A, Trombetta AC, Vanhaecke A, Smith V. Reliability of simple capillaroscopic definitions in describing capillary morphology in rheumatic diseases. *Rheumatology (Oxford)* 2018; 57 (4): 757–9.
18. Smith V, Beeckman S, Herrick AL, Decuman S, Deschepper E, De Keyser F, Distler O, Foeldvari I, Ingegnoli F, Müller-Ladner U, Riccieri V, Riemekasten G, Sulli A, Voskuyl A, Cutolo M, EULAR study group on microcirculation. An EULAR study group pilot study on reliability of simple capillaroscopic definitions to describe capillary morphology in rheumatic diseases. *Rheumatol (Oxford)* 2016; 55 (5): 883–90.
19. Rajaei A, Dehghan P, Delkash P. Reporting microvascular changes in nail fold capillaroscopy: A narrative review. *Rheumatol Res* 2016; 1 (1): 43–50.
20. Rosato E, Gigante A, Barbano B, Cianci R, Molinaro I, Pisarri S, Salsano F. In systemic sclerosis macrovascular damage of hands digital arteries correlates with microvascular damage. *Microvasc Res* 2011; 82 (3): 410–5.
21. Nietert P, Shaftman S, Silver R, Wolf B, Egan B, Hunt K, et al. Raynaud phenomenon and mortality: 20+ years of follow-up of the Charleston Heart Study cohort. *Clin Epidemiol* 2015; 7: 161.
22. Inoue T, Matsuoka H, Higashi Y, Ueda SI, Sata M, Shimada KE, Ishibashi Y, Node K. Flow-mediated vasodilation as a diagnostic modality for vascular failure. *Hypertens Res* 2008; 31: 2105–13.
23. Deanfield JE, Halcox JP, Rabelink TJ. Endothelial function and dysfunction: Testing and clinical relevance. *Circulation* 2007; 115 (10): 1285–95.
24. Lerman A, Zeiher AM. Endothelial function: Cardiac events. *Circulation* 2005; 111 (3): 363–8.
25. Moerland M, Kales AJ, Schrier L, Van Dongen MGJ, Bradnock D, Burggraaf J. Evaluation of the endoPAT as a tool to assess endothelial function. *Int J Vasc Med* 2012; 2012: 904141.
26. Matsuzawa Y, Li J, Aoki T, Guddeti RR, Kwon TG, Cilluffo R, Widmer RJ, Gulati R, Lennon RJ, Lerman LO, Lerman A. Predictive value of endothelial function by noninvasive peripheral arterial tonometry for coronary artery disease. *Coron Artery Dis* 2015; 26 (3): 231–8.

27. Bonetti PO, Lerman LO, Lerman A. Endothelial dysfunction: A marker of atherosclerotic risk. *Arterioscler Thromb Vasc Biol* 2003; 23 (2): 168–75.
28. Axtell AL, Gomari FA, Cooke JP. Assessing endothelial vasodilator function with the Endo-PAT 2000. *J Vis Exp* 2010; 44: 2167.
29. Kuvin JT, Patel AR, Sliney KA, Pandian NG, Sheffy J, Schnall RP, Karas RH, Udelson JE. Assessment of peripheral vascular endothelial function with finger arterial pulse wave amplitude. *Am Heart J* 2003; 146 (1): 168–74.
30. Hamburg NM, Benjamin EJ. Assessment of Endothelial Function Using Digital Pulse Amplitude Tonometry. *Trends Cardiovasc Med* 2009; 19 (1): 6-11.
31. Itamar Medical Ltd. EndoPAT™2000 Device User Manual 2002. Available at <https://www.itamar-medical.com/wp-content/uploads/2019/07/OM1695214.pdf>.
32. Kasap-Cuceoglu M, Pehlivan-turk-Kizilkan M, Sag E, Sener S, Balik Z, Akgul S, Derman O, Bilginer Y, Kanbur N, Özen S. AB0737 The nail fold capillaroscopic findings of adolescents with anorexia nervosa and bulimia nervosa. *Ann Rheum Dis* 2021; 80 (Suppl 1): 1398.
33. Taher R, Sara JD, Toya T, Shepherd R, Moder K, Lerman LO, Lerman A. Secondary Raynaud's phenomenon is associated with microvascular peripheral endothelial dysfunction. *Microvasc Res* 2020; 132: 104040.
34. Rollando D, Bezante GP, Sulli A, Balbi M, Panico N, Pizzorni C, Negrini S, Brunelli C, Barsotti A, Cutolo M, Indiveri F, Ghio M. Brachial artery endothelial-dependent flow-mediated dilation identifies early-stage endothelial dysfunction in systemic sclerosis and correlates with nailfold microvascular impairment. *J Rheumatol* 2010; 37 (6): 1168–73.
35. Springall GAC, Caughey M, Zannino D, Kyprianou K, Mynard JP, Rudolph S, Cheong J, Yeo M, Cheung MMH. Long-term cardiovascular consequences of adolescent anorexia nervosa. *Pediatr Res* 2023; online ahead of print.

Received: June, 16, 2023

Accepted: July, 11, 2023