Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Medical Hypotheses 144 (2020) 110229

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Non-invasive assessment of endothelial dysfunction: A novel method to predict severe COVID-19?

Sarangini Yoganandamoorthy[a,*], M.A.D.S.N. Munasinghe[a], L.V.U. Wanigasuriya[a], M.K.K. Priyankara[b], Saroj Jayasinghe[a]

[a] Faculty of Medicine, University of Colombo, Kynsey Road, Colombo 00800, Sri Lanka
[b] University of Moratuwa, Jendo Innovations (Pvt) Ltd, Sri Lanka

ARTICLE INFO

Keywords:
SARS-CoV-2
COVID-19
Endothelial dysfunction
Technology
Management

ABSTRACT

The COVID-19 pandemic caused by the SARS-CoV-2 virus has infected millions and overburdened the healthcare infrastructure globally. Recent studies show that the endothelial dysfunction caused by the virus contributes to its high morbidity and mortality. A parameter that can identify patients who will develop complications early will be valuable in patient management and reducing the burden on medical resources. An emerging technology is currently being tested to predict the cardiovascular risk via non-invasively measuring the endothelial dysfunction. This paper reviews how the assessment of endothelial dysfunction using this technology can be used as a potential parameter in the prognostication and management of COVID-19 patients.

Introduction

COVID-19 is an ongoing pandemic that has devasted several countries. As of the 12th of August 2020, a total of 20,162,474 confirmed cases of COVID-19 have been reported to the WHO, and this includes 737,417 deaths. The highest number of cases so far have been reported from the North and South American region, while the European region currently comes in second. The USA has reported the highest number of cases so far with 5,039,709 confirmed cases, while Brazil comes in second with a total of 3,057,470 confirmed cases and India comes in third with 2,329,638 cases [1].

The key pathogenesis proposed for COVID-19 is an antibody enhanced cytokine storm and endothelial damage [2,3]. Several countries have been overburdened by the number of patients who require intensive care leading to deaths due to resource limitations. A prognostic predictor may help solve this by identifying patients who are likely to become severe and directing the limited resources to them [4,5].

Currently, technology that can non-invasively detect endothelial dysfunction is being studied in many countries with regard to their place in assessing cardiovascular risk. This paper proposes how this technology could be used in the prognostication and management of COVID-19 patients.

Pathogenesis OF COVID-19

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus, enters the lungs, and binds to the Angiotensin-Converting Enzyme 2 (ACE2) receptors in the alveolar cells of the pulmonary tissue [2,3,6–8]. Once the virus binds to the receptor, it is internalized by endocytosis [6] and produces viral particles that are released into the surrounding tissue by cell destruction [7]. They either directly enter into the Antigen Presenting Cells (APC) (e.g. s dendritic cells and macrophages) or are phagocytosed while within infected cells by macrophages [9]. These APCs activate the B lymphocytes to differentiate into plasma cells which produce specific antibodies against the virus via CD4 cells in the regional lymph nodes [7,9].

Specific antibody production leads to a condition known as “antibody enhanced cytokine storm” where these antibodies facilitate the phagocytosis of the virus and it further activates macrophages to produce excess cytokines such as Interleukin (IL)-2, IL-6, Tumor Necrosis Factor (TNF). This uncontrolled inflammatory reaction worsens the patient’s condition by causing local and systemic damage [2,9].

The initial focus of the pathogenesis of COVID-19 was on this Cytokine Storm. However, recent studies are more focused on endothelial damage and dysfunction [3,6–8]. Endothelial dysfunction is defined as “*a systemic condition in which the endothelium loses its physiological properties, including the tendency to promote vasodilation, fibrinolysis, and anti-aggregation.*” [8] Findings such as arterial and venous

* Corresponding author.
E-mail addresses: sarangini.y@gmail.com (S. Yoganandamoorthy), keerthi@effectivesolutions.lk (M.K.K. Priyankara), saroj@clinmed.cmb.ac.lk (S. Jayasinghe).

https://doi.org/10.1016/j.mehy.2020.110229
Received 13 August 2020; Accepted 28 August 2020
Available online 02 September 2020
0306-9877/ © 2020 Elsevier Ltd. All rights reserved.

thrombosis leading to microthrombi formation [3,7], high Von Willebrand factor levels, and Computed Tomography (CT) findings of extensive vascular damage demonstrate the involvement of endothelial injury in the pathogenesis of COVID-19 [3,6,7].

In COVID-19 endothelial damage can occur in several ways. It is theorized that this viral infection downregulates the ACE2 receptors in the pulmonary tissue [6] disturbing the Renin-Angiotensin System, enhancing inflammation and increasing vascular permeability [2]. As ACE2 is also seen in endothelial tissue across all organs, an aggressive immune response causes widespread injury to the endothelium. Elevated levels of cytokines act on the endothelium dampening its antithrombotic action which activates the coagulation system causing thrombosis [3,6]. Accumulations of inflammatory cells in the endothelium lead to an endothelitis and apoptosis of endothelial cells ultimately resulting in endothelial dysfunction. [10,11]

Nitric Oxide (NO) plays a role in the pathogenesis of COVID-19. Suppression of Nitric Oxide Synthase and preexisting low levels of Nitric Oxide in the endothelium contribute to the endothelial dysfunction [12,13].

Therefore, emerging studies suggest that COVID-19 disease pathogenesis is not only related to the immune response but also associated with widespread endothelial dysfunction and endothelitis leading to complications [3,6,10,13–16].

Technology to detect endothelial dysfunction

Several non-invasive methods are available to assess endothelial dysfunction. The underlying principle of these methods is the analyses of the pulse wave forms of blood flow. The pulse wave produced when blood is pumped into the aorta, rises in systole and falls during diastole. This diastolic drop is interrupted by a bump called the diastolic wave due to the reflection of the pulse wave from "*branching points and resistance vessels*", creating the asymmetric shape of the wave with the dicrotic notch [17,18]. Early return of this wave in endothelial dysfunction changes the shape of the pulse wave and leads to the disappearance of the dicrotic notch [19–21].

One method is to use Photoplethysmography (PPG) to non-invasively assess the shape or contour of the waveform of the peripheries.

Another non-invasive method is to measure the change in temperature before, during and after occlusion of blood flow to the arm using a blood pressure cuff. The occlusion of blood flow results in temperature drop and release of the blood flow produces a response known as " Reactive Hyperaemia"—a quick vasodilatory response due to increased Nitric Oxide (NO) production in the endothelial cells [22]. Decreased NO production that is involved in endothelial dysfunction and cardiovascular disease, leads to a slower rise in temperature [23].

Above changes in parameters of the pulse pressure wave and the temperature graph are analysed via machine learning software that uses Artificial Intelligence-based technology to assess the level of endothelial dysfunction [21,24].

Other than these, invasive methods such as "*intracoronary infusion of acetylcholine and quantitative angiography*"; semi-invasive methods such as brachial artery plethysmography after infusion of acetylcholine; and non- invasive methods such as brachial artery plethysmography, flow-mediated vasodilation detected by ultrasound and finger plethysmography during reactive hyperemia, have also been used to test endothelial function [18,25].

Endothelial function is being tested by several research groups to predict cardiovascular risk [26–28]. This non-invasive test that measures endothelial dysfunction is a potential and practical option to prognosticate patients with COVID-19. We propose 3 potential uses of this artificial intelligence-based technology in COVID-19 patients: 1) to identify patients who develop endothelial dysfunction early and hence are likely to develop complications 2) to identify high-risk patients with preexisting endothelial dysfunction and 3) to monitor the response to therapy.

1) To identify patients who develop endothelial dysfunction early and hence are likely to develop complications
   Identifying patients likely to develop endothelial dysfunction due to COVID-19 infection, which is associated with severe disease, could be very important in the management of this disease.

Up to now, different scores, methods and models have been proposed to identify patients who will develop severe complications and organ failure but haven't been used in widespread clinical practice [29]. Some of the proposed prognostic parameters include age, sex, comorbidities, C reactive protein, body temperature, creatinine, D-dimer levels, white blood cell count, neutrophil count, lymphocyte count, platelet count, IL-6 and serum ferritin [8,29–32] – even artificial intelligence-based systems that use machine learning to identify high-risk patients using CT imaging of the lung have been proposed [33].

Patients who are affected by severe disease and multiple organ failure in COVID-19 develop features of thromboembolic disease and clotting disorders [8,15,34] which are also conditions shown to be linked with endothelial dysfunction.

Early prognostication will allow better monitoring and management of severely ill patients, in addition to efficient planning and allocation of resources at hospital-level[5,33] and this may be achieved by detecting the endothelial dysfunction early using this non– invasive technology.

2) To identify high-risk patients with preexisting endothelial dysfunction
   Comorbidities such as cardiovascular disease, diabetes mellitus, hypertension, male sex, smoking, obesity and increased age above 45 years have been associated with more complications, worse outcomes and higher fatality in COVID-19 [6,8,35–37]. All these conditions are associated with preexisting endothelial dysfunction [38–41] and lower endothelial Nitric Oxide levels which may predisposes to the worse outcomes in COVID-19 seen in this group of patients [10,11,13].

This technology can be used to identify these high-risk patients before they develop complications. Hence they can be managed in a more intensive setting.

3) To monitor the response to therapy
   Currently, there is no specific therapy for COVID-19 [35,42]. Various treatment including antivirals, anti-inflammatory drugs, antimalarials have been tested, but the research and trials on treatment are continuously evolving [43]. Targeting endothelial function has also been proposed as a potential treatment option [44]. Currently, the management of severe COVID-19 patients includes respiratory support and intensive care.

As further drugs can and will be tested in the future, the measurement of endothelial dysfunction may provide a quick, cost-effective and non-invasive method to monitor the success of these proposed therapies.

Conclusions and future research perspectives

Early prognostication of COVID-19 patients may be vital to their management. As there is increasing evidence regarding the pathophysiology of COVID-19 linked to endothelial dysfunction and endothelitis, there is also a possibility that preexisting subclinical endothelial dysfunction may be associated with worse outcomes in patients who have not been previously diagnosed with cardiovascular disease, diabetes mellitus and hypertension. The application of this promising technology to non-invasively detect endothelial dysfunction needs to be studied further with regards to improving the management and prognostication of COVID-19 patients.

Ethical Approval and Informed Consent

Not relevant.

Financial support and disclosures

Personal funds were used to write the paper.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

Elective Committee, Faculty of Medicine, University of Colombo

References

[1] WHO Coronavirus Disease (COVID-19) Dashboard | WHO Coronavirus Disease (COVID-19) Dashboard n.d. https://covid19.who.int/?gclid=CjwKCAjwps75BRAcEiwAEiACMWvC7Hp55kZYSYJGowSlJhga9F-PtKaymACK03sF-4HZiJxyhmr_1hoCqlwQAvD_BwE (accessed August 13, 2020).
[2] Jin Y, Yang H, Ji W, Wu W, Chen S, Zhang W, et al. Virology, epidemiology, pathogenesis, and control of COVID-19. Viruses 2020;12:372. https://doi.org/10.3390/v12040372.
[3] Pons S, Fodil S, Azoulay E, Zafrani L. The vascular endothelium: the cornerstone of organ dysfunction in severe SARS-CoV-2 infection. Crit Care 2020;24:353. https://doi.org/10.1186/s13054-020-03062-7.
[4] Seitz R, Schramm W. DIC in COVID-19: implications for prognosis and treatment? J Thromb Haemost 2020;18:1798–9. https://doi.org/10.1111/jth.14878.
[5] Gong J, Ou J, Qiu X, Jie Y, Chen Y, Yuan L, et al. A tool for early prediction of severe coronavirus disease 2019 (COVID-19): a multicenter study using the risk Nomogram in Wuhan and Guangdong, China. Clin Infect Dis 2020;71:833–40. https://doi.org/10.1093/cid/ciaa443.
[6] Amraei R, Rahimi N. COVID-19 renin-angiotensin system and endothelial dysfunction. Cells 2020;9:1652. https://doi.org/10.3390/cells9071652.
[7] Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: a review. Clin Immunol 2020;215:108427. https://doi.org/10.1016/j.clim.2020.108427.
[8] Sardu C, Gambardella J, Morelli MB, Wang X, Marfella R, Santulli G. Hypertension, thrombosis, kidney failure, and diabetes: is COVID-19 an endothelial disease? A comprehensive evaluation of clinical and basic evidence. J Clin Med 2020;9:1417. https://doi.org/10.3390/jcm9051417.
[9] Wang J, Jiang M, Chen X, Montaner LJ. Cytokine storm and leukocyte changes in mild versus severe SARS-CoV-2 infection: review of 3939 COVID-19 patients in China and emerging pathogenesis and therapy concepts. J Leukoc Biol 2020;108:17–41. https://doi.org/10.1002/JLB.3COVR0520-272R.
[10] Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet 2020;395:1417–8. https://doi.org/10.1016/S0140-6736(20)30937-5.
[11] Mosleh W, Chen K, Pfau SE, Vashist A. Endotheliitis and endothelial dysfunction in patients with COVID-19: its role in thrombosis and adverse outcomes. J Clin Med 2020;9:1862. https://doi.org/10.3390/jcm9061862.
[12] Martel J, Ko Y-F, Young JD, Ojcius DM. Could nasal nitric oxide help to mitigate the severity of COVID-19? Microbes Infect 2020;22:168–71. https://doi.org/10.1016/j.micinf.2020.05.002.
[13] Green SJ. Covid-19 accelerates endothelial dysfunction and nitric oxide deficiency. Microbes Infect 2020;22:149–50. https://doi.org/10.1016/j.micinf.2020.05.006.
[14] Leisman DE, Deutschman CS, Legrand M. Facing COVID-19 in the ICU: vascular dysfunction, thrombosis, and dysregulated inflammation. Intensive Care Med 2020;46:1105–8. https://doi.org/10.1007/s00134-020-06059-6.
[15] Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up. J Am Coll Cardiol 2020;75:2950–73. https://doi.org/10.1016/j.jacc.2020.04.031.
[16] De Lorenzo A, Escobar S, Tibiriçá E. Systemic endothelial dysfunction: a common pathway for COVID-19, cardiovascular and metabolic diseases. Nutr Metab Cardiovasc Dis 2020;30:1401–2. https://doi.org/10.1016/j.numecd.2020.05.007.
[17] Herring N, Paterson D. Levick's introduction to cardiovascular physiology. 6th ed. CRC Press; 2018.
[18] Arrebola-Moreno AL, Laclaustra M, Kaski JC. Noninvasive assessment of endothelial function in clinical practice. Rev Española Cardiol (English Ed) 2012;65:80–90. https://doi.org/10.1016/j.rec.2011.10.004.
[19] Dawber TR, Thomas HE, Mcnamara PM. Characteristics of the dicrotic notch of the arterial pulse wave in coronary heart disease. Angiology 1973;24:244–55. https://doi.org/10.1177/000331977302400407.
[20] Lax H, Feinberg AW, Cohen BM. Studies of the arterial pulse wave: I. The normal pulse wave and its modification in the presence of human arteriosclerosis. J Chronic Dis 1956;3:618–31. https://doi.org/10.1016/0021-9681(56)90158-8.
[21] Millasseau SC, Ritter JM, Takazawa K, Chowienczyk PJ. Contour analysis of the photoplethysmographic pulse measured at the finger. J Hypertens 2006;24:1449–56. https://doi.org/10.1097/01.hjh.0000239277.05068.87.
[22] Ahmadi N, Nabavi V, Nuguri V, Hajsadeghi F, Flores F, Akhtar M, et al. Low fingertip temperature rebound measured by digital thermal monitoring strongly correlates with the presence and extent of coronary artery disease diagnosed by 64-slice multi-detector computed tomography. Int J Cardiovasc Imaging 2009;25:725–38. https://doi.org/10.1007/s10554-009-9476-8.
[23] Kharalkar N, Valvano JW, Naghavi M, Wei Chia Ling. Novel temperature based technique for measurement of endothelial dysfunction. Proc. 25th Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. (IEEE Cat. No.03CH37439) IEEE; 2003. p. 308–11. https://doi.org/10.1109/IEMBS.2003.1279623.
[24] van der Wall EE, Schuijf JD, Bax JJ, Jukema JW, Schalij MJ. Fingertip digital thermal monitoring: a fingerprint for cardiovascular disease? Int J Cardiovasc Imaging 2010;26:249–52. https://doi.org/10.1007/s10554-009-9552-0.
[25] Flammer AJ, Anderson T, Celermajer DS, Creager MA, Deanfield J, Ganz P, et al. The assessment of endothelial function. Circulation 2012;126:753–67. https://doi.org/10.1161/CIRCULATIONAHA.112.093245.
[26] JENDO INNOVATIONS n.d. http://www.jendoinnovations.com/ (accessed July 24, 2020).
[27] Angioscan: Diagnosis of heart and blood vessels diseases, medical equipment for home n.d. https://www.angioscan.ru/en/ (accessed July 24, 2020).
[28] Endothelix / VENDYS2 n.d. https://www.endothelix.com/ (accessed July 24, 2020).
[29] Wynants L, Van Calster B, Bonten MMJ, Collins GS, Debray TPA, De Vos M, et al. Prediction models for diagnosis and prognosis of covid-19 infection: systematic review and critical appraisal. BMJ 2020:369. https://doi.org/10.1136/bmj.m1328.
[30] Spiezia L, Boscolo A, Poletto F, Cerruti L, Tiberio I, Campello E, et al. COVID-19-related severe hypercoagulability in patients admitted to intensive care unit for acute respiratory failure. Thromb Haemost 2020;120:998–1000. https://doi.org/10.1055/s-0040-1710018.
[31] Henry BM, de Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chem Lab Med 2020;58:1021–8. https://doi.org/10.1515/cclm-2020-0369.
[32] Zheng Y, Zhang Y, Chi H, Chen S, Peng M, Luo L, et al. The hemocyte counts as a potential biomarker for predicting disease progression in COVID-19: a retrospective study. Clin Chem Lab Med 2020;58:1106–15. https://doi.org/10.1515/cclm-2020-0377.
[33] Zhang K, Liu X, Shen J, Li Z, Sang Y, Wu X, et al. Clinically applicable AI system for accurate diagnosis, quantitative measurements, and prognosis of COVID-19 pneumonia using computed tomography. Cell 2020;181(1423–1433):e11https://doi.org/10.1016/j.cell.2020.04.045.
[34] Zhang Y, Xiao M, Zhang S, Xia P, Cao W, Jiang W, et al. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. N Engl J Med 2020;382:e38https://doi.org/10.1056/NEJMc2007575.
[35] Guzik TJ, Mohiddin SA, Dimarco A, Patel V, Savvatis K, Marelli-Berg FM, et al. COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis, and treatment options. Cardiovasc Res 2020;116:1666–87. https://doi.org/10.1093/cvr/cvaa106.
[36] Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. Int J Infect Dis 2020;94:91–5. https://doi.org/10.1016/j.ijid.2020.03.017.
[37] Froldi G, Dorigo P. Endothelial dysfunction in Coronavirus disease 2019 (COVID-19): gender and age influences. Med Hypotheses 2020;144:110015https://doi.org/10.1016/j.mehy.2020.110015.
[38] Perticone F, Ceravolo R, Pujia A, Ventura G, Iacopino S, Scozzafava A, et al. Prognostic significance of endothelial dysfunction in hypertensive patients. Circulation 2001;104:191–6. https://doi.org/10.1161/01.CIR.104.2.191.
[39] Lerman A, Zeiher AM. Endothelial function. Circulation 2005;111:363–8. https://doi.org/10.1161/01.CIR.0000153339.27064.14.
[40] Sena CM, Pereira AM, Seiça R. Endothelial dysfunction — a major mediator of diabetic vascular disease. Biochim Biophys Acta - Mol Basis Dis 2013;1832:2216–31. https://doi.org/10.1016/j.bbadis.2013.08.006.
[41] Bonetti PO, Lerman LO, Lerman A. Endothelial dysfunction: a marker of atherosclerotic risk. Arterioscler Thromb Vasc Biol 2003;23:168–75. https://doi.org/10.1161/01.ATV.0000051384.43104.FC.
[42] Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nat Rev Drug Discov 2020;19:149–50. https://doi.org/10.1038/d41573-020-00016-0.
[43] Pascarella G, Strumia A, Piliego C, Bruno F, Del Buono R, Costa F, et al. COVID-19 diagnosis and management: a comprehensive review. J Intern Med 2020;288:192–206. https://doi.org/10.1111/joim.13091.
[44] Gustafson D, Raju S, Wu R, Ching C, Veitch S, Rathnakumar K, et al. Overcoming barriers. Arterioscler Thromb Vasc Biol 2020;40:1818–29. https://doi.org/10.1161/ATVBAHA.120.314558.