



Long COVID in Pediatric and Young Adult Patients: A Review of Evaluation for Microvascular Changes, Endothelial Dysfunction, and Arterial Stiffness

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ABSTRACT

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) reservoirs in most tissues may be underlying endotheliitis in Post-Acute Sequelae of SARS-CoV-2 Infection (PASC). The vascular changes of the microcirculation with persistent capillary rarefaction and endothelial dysfunction have already been demonstrated in adult patients with PASC. In this review, the author outlined the current knowledge and trends of long COVID-19 for evaluation of microvascular changes, endothelial dysfunction and arterial stiffness in pediatric and young adult patients. The Medical Literature Analysis and Retrieval System Online (MEDLINE)/PubMed and Excerpta Medica dataBASE (EMBASE) data-bases were systematically searched for studies using microvascular, endothelial, and Arterial Stiffness (AS) dysfunction in pediatric and young adult patients with long COVID. In addition, the therapeutic strategies for long COVID patients have been also described. Based on the evidence, Nailfold Videocapillaroscopy (NVC) may demonstrate microvascular injury such as capillary dilatations in adult patients with long COVID. The increased arterial stiffness may lead to atherosclerosis status, increased vascular aging, Cardiovascular Disease (CVD) risks, and CV complications in pediatric and young adult patients with long COVID. As the increasing AS may tend to cause the hypertension and atherosclerotic condition in the long term in pediatric and young long COVID patients, therefore it is emphasized that the comprehensive follow-up for early onset of atherosclerosis condition is essential. Further investigations are needed to clarify the outcomes.

Key words: Long COVID; Microvascular dysfunction; Arterial stiffness; Endothelial dysfunction; Defibrotide; Post-Acute Sequelae of SARS-CoV-2 Infection (PASC).

INTRODUCTION

SARS-CoV-2 reservoirs in most tissues may be underlying endotheliitis in PASC suggesting the prolonged viral fecal shedding is a potential feature for developing of PASC [1]. The virus persistence, inflammation, endothelial dysfunction, thrombosis, autoimmunity, dysbiosis and gut translocation, latent virus reactivation, and mitochondrial dysfunction have been regarded as the pathogenesis of long COVID [2]. From multicenter retrospective study, NVC examination in patient with long COVID exhibited significant microvascular injury compared with control participants [3]. Previous study provided the variability in AS and endothelial dysfunction after COVID-19 infection in adult patients after 18 months follow

ups from systematic review and meta-analysis [4]. The vascular changes of the microcirculation with persistent capillary rarefaction and endothelial dysfunction have already been demonstrated in adult patients with PASC [5]. While, recent study indicated microvascular injury such as microvascular reduction using sublingual Sidestream Dark Field (SDF) and increased AS by peripheral arterial tonometry (Endo-PAT) in pediatric patient with long COVID [5]. In this review, the current knowledge of long COVID for evaluation of microvascular changes, endothelial dysfunction and arterial stiffness has been outlined in pediatric and young adult patients with long COVID. In addition, the therapeutic strategies for long COVID have been also explored.

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LITERATURE REVIEW

Endothelial dysfunction in acute COVID-19 and PASC, or long COVID in adult patients

COVID-19 may be a systemic endothelial disease or a multi-organ disease including endotheliitis, hypercoagulability, and cytokine storm especially in severe stage as previously described [6]. With respect to the SARS-CoV-2 Omicron variant, the report emphasized the importance of estimation of the endothelial function evaluated by Flow-Mediated Vasodilation (FMD) test because this strain exhibited more efficient transduction of Angiotensin-Converting Enzyme (ACE2)-expressing target cells, leading to endothelial dysfunction [7]. The position paper recommended that the endothelial biomarkers and function such as FMD should be assessed for their usefulness of the risk stratification in patients with COVID-19 [8]. It has been proposed that Flow-Mediated Vasodilation (FMD) and Nitroglycerin-Mediated Vasodilation (NMD) in the brachial artery are potential procedures for assessing vascular endothelial and Vascular Smooth Muscle Cell (VSMC) function in atherosclerosis status [9-11]. It is known that following acute COVID-19 infection, a patient with clinical presentations lasting longer than 12 weeks is considered as Long COVID, chronic COVID syndrome or PASC [12]. Jud, et al. demonstrated that COVID-19 may affect arterial stiffness, capillary morphology, Endothelial Microparticles (EMP), parameters of arginine, kynurenine and homocysteine metabolism, and inflammation subsequently leading to COVID-19-related endothelial dysfunction and inflammatory vasculopathy in patients 6 months after SARS-CoV-2 infection [13]. Previous study suggested that the severe inflammation in COVID-19 may affect microvascular dysfunction and contribute to persistent inflammation after COVID-19 infection. It is plausible that the sustained endothelial dysfunction and arterial stiffness along with high oxidative stress may lead to cardiac manifestations after COVID-19 infection. Due to prolonged endothelial dysfunction and inflammation, the impaired FMD, along with the increased Pulse Wave Velocity (PWV) may be associated with the severity and duration of inflammatory process in COVID-19 patients with persistent clinical manifestations and inflammatory biomarkers, thereby suggesting that the early onset of atherosclerosis in non-CVD patients and CV outcomes in preexisting CVD patients after COVID-19 are warranted as previously described [14].

Essential mechanisms underlying long COVID or PASC

Fatigue, shortness of breath, and cognitive dysfunction and so on are common clinical symptoms in PASC. PASC has been exhibited to be related to several findings of endothelial damage [15]. This prolonged microvascular endotheliitis showed characteristic features of elevated von Willebrand factor (vWF), endothelial colony-forming cells, and fibrinolysis-resistant microclots leading to localized inflammation and autoantibody activation, and microvascular thrombosis [16]. Broad presences of this virus in multiple organs including brain, heart, and skin have been shown in autopsy finding of acute COVID-19

patients. Though the evidence suggested that the virus persists in adults, the previous study also indicated the viral persistence in pediatric patient with infected with SARS-CoV-2 [17]. Three months following the acute SARS-CoV-2 infection, the presence of SARS-CoV-2 nucleocapsid proteins in the intestinal lamina propria was detected in pediatric patient with sustained gastrointestinal findings [18]. Another study showed that SARS-CoV-2 was observed of two young patients in a mesenteric lymph node and in the ileum by immunofluorescence [19]. SARS-CoV-2 reservoirs in most tissues may be regarded as underlying endotheliitis in pathogenesis of PASC [1]. The persistent viral fecal shedding is an essential finding for development of PASC [1]. SARS-CoV-2 RNA fragments have been observed in 25% of PASC or long COVID patients [20]. The circulating SARS-CoV-2 RNA fragments are a significant finding of PASC, similarly, soluble Spike (S) and Nucleocapsid (N) proteins and viral Pathogen-Associated Molecular Patterns (PAMPs) may be epiphenomena in endothelial cell damage [1]. It has been proposed that cryptic reservoirs of SARS-CoV-2 in multiple tissues, effecting by direct endothelial cell infection, release of soluble viral products, infection of monocytes adjacent to the vasculature, or activation of other viruses lead to cytopathic effects in endothelial cells as potential mechanisms of long COVID [1]. Long COVID is a newly identified as infection-associated chronic condition which causes impairment in some participants [2]. The virus persistence, inflammation, endothelial dysfunction, thrombosis, autoimmunity, dysbiosis and gut translocation, latent virus reactivation, and mitochondrial dysfunction have been indicated for the pathogenesis of long COVID [2].

Microvascular changes, endothelial dysfunction and arterial stiffness in pediatric and young adult patients with long COVID

Long-lasting microvascular changes have been noted in Multisystem Inflammatory Syndrome in Children (MIS-C) [21]. Previous report indicated the assessment of endothelial function for risk stratification, follow-up of convalescence, and prediction of autoimmune disease in patients with MIS-C [22]. According to the National Institute for Health and Care Excellence (NICE), long COVID is defined by symptoms persisting or developing after acute COVID-19, including presenting COVID-19 symptoms (from 4 to 12 weeks) and post-COVID-19 syndromes (12 weeks or more) [23]. The pathogenesis of long COVID is unclear [5]. The NVC is a potential test for examining microcirculation in Connective Tissue Diseases (CTDs) [3,24]. During the acute phase of SARS-CoV-2 microvascular injury by NVC test has been estimated showing capillary dilatations, microhemorrhage, and pericapillary edema in adult patients [25]. Previous study in long COVID adult patients with Primary Raynaud's Phenomenon (PRP) showed a decrease of the absolute number of capillaries has been exhibited [26]. In a NVC test, capillary alterations were also more frequently found during the post-COVID-19 than patients with Atherosclerosis CV Disease (ASCVD) and healthy controls [4,13]. From multicentre retrospective study, NVC examination in patient with long COVID after 12 months exhibited significant microvascular injury including the dilated capillaries,

microhemorrhage, abnormal shapes, and decreased capillary density compared with control participants [3]. Macrovascular thrombosis is a characteristic of acute COVID-19, while the changes of microvascular have already been demonstrated in adult patients with long COVID or PASC [27]. Based on the evidence, NVC may demonstrate microvascular injury such as capillary dilatations both during acute phase and long-term phase of SARS-CoV-2 infection in adult patients. Recent study exhibited that microvascular changes, endothelial dysfunction, and established contributors to SARS-CoV-2-associated conditions such as MIS-C in pediatric patients with long COVID [5]. Microcirculation study exhibited by Sidestream Dark Field (SDF) imaging with the Microvascular Flow Index: MFI ($p=0.003$), Total Vessel Density: TVD ($p<0.001$), and the Proportion of Perfused Vessels: PPV ($p<0.001$), whereas endothelial dysfunction and arterial stiffness were assessed by Endo-PAT with Reactive Hyperemia Index: RHI ($p=0.439$) and Augmentation Index: AIX75 ($p=0.008$) using multivariate linear regression [5]. The results indicated microvascular injury such as microvascular reduction using sublingual SDF and increased AS by Endo-PAT in pediatric patient with long COVID [5]. The study also suggested that damaged microcirculation and increased AS may tend to cause the hypertension and atherosclerotic condition in the long term in pediatric patients with long COVID [5]. While, pediatric Endo-PAT studies have generally been used children >10 years and adolescents [28]. Karaviti, et al. have statistically demonstrated the increased PWV in patients with disease history compared with healthy controls but after adjusting confounding factors, vascular difference was not observed [29]. While, the soluble Soluble intercellular adhesion molecule-1 (ICAM-1) levels statistically increased in patients with a history of moderate/severe COVID-19 infection compared with controls indicating the endothelial activation. Meanwhile, long COVID symptoms including general fatigue, shortness of breath during exercise, and arrhythmia were detected in approximately one-quarter of the patients [29]. A few studies have been shown that the sustained symptoms are related to prolonged effects of COVID-19 among pediatric and young participant from a systematic review and meta-analysis [30]. Previous study described that processes with several months of recovery from SARS-CoV-2 infection may be necessary to improve arterial stiffness in the young adult patients [31]. Province, et al. examined FMD and Reactive Hyperemia (RH) for six months in young adults following SARS-CoV-2 infection showing some improvements in FMD but not in RH reflecting microvascular dysfunction, suggesting that the results showed the

persistent ramifications for cardiovascular condition [32]. Peng, et al. studied endothelial dysfunction by FMD and arterial stiffness using Ankle-Brachial Index (ABI), Brachial-Ankle Pulse Wave Velocity (baPWV), Carotid-Femoral Pulse Wave Velocity (cfPWV), HR, and Blood Pressure (BP) [33]. They showed that COVID-19 infection has prolonged adverse effects including endothelial function, arterial stiffness, and blood pressure within 2 to 5 months in college students showing that arterial stiffness tends to improve, but BP may not improve [33]. AS is evaluated using a PWV measurement including ABI, baPWV, cfPWV, HR, and BP and is clearly associated with vascular aging [33]. Vascular aging has a characteristic feature of higher SBP, leading to endothelial dysfunction, subsequently resulting in the increase of CVD risk [33]. Recent study provided the variability in AS such as cfPWV and endothelial dysfunction such as FMD after COVID-19 infection in adult patients (aged >18 years) after 18 months follow ups from systematic review and meta-analysis [4]. FMD exhibited a significant decrease during the acute/subacute phase, whereas normal state was shown in late recovery. Whereas cfPWV levels were higher than controls in acute/subacute phase and remained the increased status compared to controls in very late recovery [4]. It is known that post-COVID-19 inflammation sustains over a year after the SARS-CoV-2 infection. It can be explained that the endothelial dysfunction associated with impaired Nitric Oxide (NO) bioavailability and arterial stiffness serve as a role for the pathogenesis of atherosclerosis status, increase vascular aging, accelerate the CVD risks, and predict CV complications in COVID-19 survivors [4]. While recent report provided that microvascular dysfunction by RHI is related to increase of NT-proBNP levels over time, suggesting a promising involvement of the microvascular dysfunction in PASC pathogenesis and a potential cardiac remodeling [34]. The endothelial function such as FMD and RHI, AS including AI, ABI, cfPWV, and baPWV, and endothelial cell adhesion molecules such as ICAM-1 in pediatric and young adult patients with long COVID are shown (Tables 1, 2, and 3). Based on the evidence, increased arterial stiffness reflecting cfPWV and AIX75 have been shown in a few studies (Table 3). Similar to adult patients, the results may lead to atherosclerosis status, increased vascular aging, CVD risks, and CV complications. In result, the increasing AS may tend to cause the hypertension and atherosclerotic condition in the long term in pediatric and young patients with long COVID. In addition, only one study indicated microvascular injury such as microvascular reduction using sublingual SDF imaging with MFI, TVD, and PPV.

Table 1: Microvascular changes, endothelial dysfunction, and arterial stiffness in pediatric and young adult long COVID patients.

Study	Design	Age (SD)	Participants (N)
Boever, et al. [5]	Retrospective	13.5 (2.6)	37
Karaviti, et al. [29]	Prospective	10 (3.23)	144
Province, et al. [32]	Retrospective	21 (1.0)	12
Peng, et al. [33]	Retrospective	21.35 (1.99)	37

Table 2: Microvascular changes and endothelial dysfunction in pediatric and young adult long COVID patients.

Study	Duration	Microvascular changes (MFI, TVD, PPV)	Endothelial function (FMD, RHI)
Boever, et al. [5]	>4 weeks	MFI (p=0.003), TVD (p<0.001), PPV (p<0.001)	RHI (p=0.439), p-value ^a
Karaviti, et al. [29]	6.8 months	NA	NA
Province, et al. [32]	6 months	RH and PLM (p>0.05), p-value ^b	FMD (p<0.001), p-value ^b
Peng, et al. [33]	2 to 5 months	NA	FMD (p<0.001), p-value ^c

Note: NA: Not Applicable, MFI: Microvascular Flow Index, TVD: Total Vessel Density, PPV: Proportion of Perfused Vessel, FMD%: Flow-Mediated Vasodilation, RHI: Reactive Hyperemia Index, PLM: Hyperemic Response To Passive Limb Movement
p-value^a: Multivariate linear regression; p-value^b: Kolmogorov-Smirnov test; p-value^c: Wilcoxon signed-rank test.

Table 3: Arterial stiffness and endothelial cell adhesion molecules in pediatric and young adult long COVID patients.

Study	Arterial stiffness (AI, ABI, cfPWV, baPWV)	Endothelial cell adhesion molecule p-value ^a p-value ^b p-value ^c p-value ^d
Boever, et al. [5]	AIx75 (p=0.008), p-value ^a	NA
Karaviti, et al. [29]	AI (p=0.583); PWV (p=0.001), p-value ^b	ICAM-1 (p<0.001), p-value ^d
Province, et al. [32]	NA	NA
Peng, et al. [33]	cfPWV (p=0.022)	NA

Note: NA: Not Applicable, AI%: Augmentation index, ABI: Ankle Brachial Pressure Index, cfPWV m/s: carotid to femoral pulse index, PWV: Pulse Wave Velocity, ICAM-1 ng/mL: Intercellular Adhesion Molecules-1.

p-valued (d superscript)

p-valued: Tukey-Kramer post hoc correlation

Defibrotide for management and protection of endothelial injury in COVID-19 and PASC

Defibrotide (DF) for endothelial damage in SARS-CoV-2 infection/PASC have been shown. DF may emerge the endothelial effectiveness of SARS-CoV-2 infection by increased t-PA and TM expression, decreased vWF and Production and Activity Level of Plasminogen Activator Inhibitor-1 (PAI-1) expression, and platelet adhesion inhibition through increases in NO, Prostaglandin₁₂ (PGI₂), and Prostaglandin E₂ (PGE₂). DF may affect anti-inflammatory properties leading to modulate endothelial cell injury [35]. Previous study described that DF exhibited pleiotropic properties including anti-inflammatory, anti-thrombotic, and fibrinolytic suggesting broad endothelial protective efficacy [35]. Meanwhile, regarding the pathophysiology of hepatic sinusoidal Obstruction Syndrome/Veno-Occlusive Disease (SOS/VOD) after Hematopoietic Stem Cell Transplantation (HSCT), the injury of the sinusoidal Endothelial Cells (ECs) and hepatocytes have been demonstrated indicating the early use of defibrotide for severe SOS/VOD [36].

The evidence suggested that defibrotide for endothelial damage is the promising efficacy for SOS/VOD after HSCT even in pediatric patients [37,38]. DF may mitigate the effectiveness of endotheliitis after SARS-CoV-2 and other viral infections, indicating the promising efficacy as endothelial treatment and protection [16]. While targeting the SARS-CoV-2 reservoir in long COVID has been recommended informing by knowledge from targeting the Human Immunodeficiency Virus (HIV) reservoir, hepatitis C, other RNA viruses, and precession oncology [39].

DISCUSSION

Due to sustained endothelial dysfunction and inflammation, the early onset of atherosclerosis in non-CVD patients and CV outcomes in preexisting CVD patients after COVID-19 are warranted as previously described [14]. SARS-CoV-2 reservoirs in most tissues may be underlying endotheliitis in PASC indicating that the persistent viral fecal shedding is an essential finding for development of PASC [1]. It has been proposed that cryptic reservoirs of SRAS-CoV-2 in multiple tissues, effecting by

direct endothelial cell infection, release of soluble viral products, infection of monocytes adjacent to the vasculature, or activation of other viruses lead to cytopathic effects in endothelial cells as potential mechanisms of long COVID [1]. The vascular changes of the microcirculation with persistent capillary rarefaction and endothelial dysfunction have already been demonstrated in adult patients with PASC [5]. This article focuses on the current knowledge of long COVID for evaluation of microvascular changes, endothelial dysfunction and arterial stiffness in pediatric and young adult patients with long COVID. Additionally, the therapeutic strategies for long COVID have been also explored. Based on the evidence, NVC may demonstrate microvascular injury such as capillary dilatations in adult patients with long COVID. Only one study showed microvascular injury such as microvascular reduction using sublingual SDF imaging with MFI, TVD, and PPV in pediatric patient with long COVID. The increased arterial stiffness reflecting cPWV and Aix75 have been shown in a few studies (Table 3). The increased AS may lead to atherosclerosis status, increased vascular aging, CVD risks, and CV complications in pediatric and young adult patients with long COVID. As the increasing AS may tend to cause the hypertension and atherosclerotic condition in the long term in pediatric and young adult patients with long COVID, it is emphasized that the integrated follow-up for early onset of atherosclerosis state is significant. Further investigations are needed to clarify the outcomes in pediatric and young adult long COVID patients. Previous study described that DF exhibited pleiotropic properties including anti-inflammatory, anti-thrombotic, and fibrinolytic suggesting broad endothelial protective efficacy [35]. Regarding therapeutic strategies, DF may mitigate the effectiveness of endothelitis after SARS-CoV-2 and other viral infections, indicating the promising efficacy as endothelial therapy and protection [16]. While targeting the SARS-CoV-2 reservoir in long COVID has been recommended [39].

CONCLUSION

Microvascular injury such as capillary dilatations in adult patients with long COVID has been demonstrated. It is putative that the increased arterial stiffness may lead to atherosclerosis status, increased vascular aging, CVD risks, and CV complications even in pediatric and young adult patients with long COVID. As the increasing arterial stiffness may tend to induce the hypertension and atherosclerotic status in the long term in pediatric and young adult patients with long COVID, the author emphasizes the importance of comprehensive follow up for early onset of atherosclerosis status. Further studies are needed to verify the outcomes in pediatric and young adult long COVID patients.

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