Cardiology in the Young

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COVID-19 in children: acute endotheliopathy, but forgotten prostacyclin replacement?

Dietmar Schranz

Johann-Wolfgang-Goethe University Clinic, Frankfurt, Germany

Original Article

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Author for correspondence:
Prof. Dr. Dietmar Schranz, Pediatric Heart Center, Johann-Wolfgang Goethe University Clinic, Theodor-Stern-Kai 7, 60590 Frankfurt, Germany.
E-mails: dietmar.schranz@kgu.de; dietmar.schranz@paediat.med.uni-giessen.de

The excellent *AEPC position paper of Skaiste Sendzikaite et al. CY 2021*[1] describes the cardiovascular consequences of the highly contagious SARS-CoV2 in children, especially those with associated CHDs. The clinical symptoms of SARS-CoV2 infection in children range from asymptomatic disorders to severe (paediatric) inflammatory multisystem syndrome, which in some cases corresponds to systemic vasculitis. Immune dysregulation and pathogen-induced "cytokine storm" in COVID-19 have been described in detail.[2] Two partially overlapping phenotypes associated with severe COVID-19 infection were found: on the one hand, acute respiratory distress syndrome[3] and, on the other hand, a predominant microvascular disease, which is classified as endotheliopathy in connection with generalised coagulopathy.[4] The latter can lead to multiple (vital) organ dysfunction and ultimately to failure. Fortunately, severe symptomatic COVID-19 infection by the wild-type is rare in children. Additionally, a paediatric acute respiratory distress syndrome phenotype is less common than vasculopathy including a "Kawasaki-like" syndrome.[5] The "Alpha"-variant (B.1.1.7) or other mutations (Beta-, Gamma-, Delta-variants) seem to be more contagious and infectious, particularly in people under the age of 20 years.[6] Furthermore, the spike variants have an increased affinity of binding to human angiotensin converting enzyme 2.[7] Given the therapeutic options, it is a little too short to address especially acute cardiovascular management issues by citing a comprehensive guidance document developed for adults during the COVID-19 pandemic.[8] An important aspect that the COVID pandemic has in common with the general situation in the cardiovascular treatment of children is the lack of evidence-based data, which is why hypothesis-driven therapy is required. From my point of view, COVID-19-associated cardiovascular manifestations, in particular coronary involvement, are reminiscent of a Parvo B19 infection, which in the sense of vasculitis preferably affects the microvascular endothelial cells, followed by a secondary myocarditis phenotype.[9] This differs from a classic Kawasaki syndrome, in which the epicardial coronary arteries are preferentially affected and are rarely associated with sequalae myocarditis. However, this does not mean that initial medical treatment, including high-dose immunoglobulin therapy, should be withheld.[10] In addition, as described by the authors,[1] infants seem to have a higher risk for a more severe clinical course of a vasculitis-like infection. A fulminant acute myocardial necrosis and mononuclear cell infiltration were observed, but only rarely virus particles in myocardial tissue,[11] but certainly in the endothelium.[12] The mutant change is associated not only with a higher infectivity but obviously also with a more intense virus load. The endothelium as the primary target is more severely affected. A transient "endothelial stunning" of the "wild-type" seems to be changed to an endothelial injury, which also requires longer time for regeneration. The cardiovascular sequelae become more intense. The profile of seriously ill patients with myocarditis-like or ischaemic heart failure with reduced ejection fraction corresponding to clinical picture of tachypnoea and elevated troponin and natriuretic peptide levels appear more frequently. To what extent there is a separation or even an increased overlap with patients with a dominant phenotype of pulmonary dysfunction, which is characterised by dyspnoea and reduced arterial oxygen saturation (hypoxemia), is currently open.[13] In any case, knowledge about the entry, replication, and innate immune activation of viruses has increased, including the involvement of several distinct Toll-like-receptors and subsequent pathways in SARS-CoV-2 pathogenesis.[14] With regard to the consequences of COVID-19-associated endothelial disease, however, the therapeutic potential has not been fully exploited. It can be postulated that COVID endotheliopathy leads to an inhibition of the innate endothelial nitric oxide-synthetase-dependent production of nitric oxide and in particular cyclooxygenase-related prostacyclin production with subsequent hypercoagulopathy and finally vascular obstruction.[12,15] In-situ thrombosis formation can be monitored by elevated D-dimer levels, which are closely linked to mortality and morbidity.[16] In this pathophysiological context, the therapeutic potentials of prostacyclin currently seem to receive too less attention.[17,18] The guidelines do not recommend a therapeutic replacement of substances, which are lacking due to endogenous endothelial dysfunction or even damage.[1,8,17] In contrast to a disrupted endothelial nitric oxide pathway, prostacyclin can easily be replaced since it has been available for decades. From the paediatric point of view, prostacyclin is available as ilomedin or epoprostenol both administrable by continuous intravenous infusion at doses of 1–2 ng/kg/minute or 5-(10) ng/kg/minute, respectively. This dose range is safe, but effective. It can be monitored by subsequent decrease

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of D-dimer and concerning the coronary involvement by falling troponin levels. Based on previous experience with prostacyclin treatment in life-threatening paediatric "purpura fulminans", partly together with substitution of activated protein-C,[19] we also used successfully ilomedin, but currently only anecdotally in infants with paediatric inflammatory multisystem syndrome (PIMS). It can be hypothesised that prostacyclin infusion is a promising replacement therapy, suitable for COVID-19-associated microvascular diseases with thrombotic and ischaemic consequences. Prostacyclin combines platelet inhibition and support of microvascular function, which is not limited to pulmonary circulation. A Danish study on the use of ilomedin (1 ng/kg/min) in COVID-patients is planned and already started in adults.[20] In contrast to prostacyclin, which is not yet generally used, low-dosed acetyl salicylic acid has proven to be beneficial in moderately to severely ill COVID-19 patients, if prophylactically applicated.[21] Adapted to follow-up treatment for Kawasaki syndrome and from COVID-19 patients with a history of elevated troponin-I and D-dimer levels, low-dose aspirin (1–2 mg kg once a day) is recommended for follow-up treatment for 3–6 months.[22] In patients with an additional myocarditis phenotype, we also combine low-dose aspirin with clopidogrel for 3 months, which is not proved, yet.

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