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EDITORIAL COMMENT

Thrombotic and Bleeding Profile of Adults With Congenital Heart Disease Infected With COVID-19*

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Over the last 3 years, COVID-19 has become the modern worldwide pandemic, posing essential challenges for physicians who treat patients with chronic medical conditions. The responsible virus, SARS-CoV-2, although mainly causing upper and/or lower respiratory tract infection, has proven to affect all major organs.[1] Arterial and venous thrombotic events as well as bleeding complications are common clinical manifestations of COVID-19 associated with a poor outcome.[2,3] Possible pathophysiologic mechanisms are systemic inflammation, endothelial dysfunction triggered by viral invasion and blood stasis, creating a coagulopathy substrate (**Figure 1**).

It is well known that adults with congenital heart disease (ACHD) are inherently prone to thromboembolic events (TE) events with a significantly higher incidence compared to the general population.[4] The increased thrombotic risk of this population has a multifactorial etiology, related to prior surgical and/or transcatheter procedures, persistent/residual shunts, intracardiac devices, primary valvular heart disease, and potential development of atrial arrhythmias.[5] Notably, TE events as well as bleeding complications seem to be more prevalent in complex anatomies such as cyanotic congenital heart disease (CHD), Eisenmenger physiology or Fontan palliation.[6,7] In this setting a subsequent COVID-19 infection could further increase the thrombotic burden, necessitating a careful, multidisciplinary and individualized management.[8]

In this issue of *JACC: Advances*, Fusco et al[9] presented the results of an international, multicenter retrospective cohort study, aiming to describe the prevalence of TE and bleeding complications among 1,988 ACHD patients (hospitalized and ambulatory) infected with COVID-19 and identify potential risk factors for these events. TE events included a broad spectrum of ischemic cerebrovascular accident/transient ischemic attack, systemic or pulmonary embolism, deep vein or intracardiac thrombosis, and myocardial infarction, while major bleeding events were defined according to the International Society of Thrombosis and Haemostasis criteria. Fusco et al[9] demonstrated an overall prevalence of 1.5% (n = 30) for TE/bleeding events among ACHD patients, which appears to be similar to other non-ACHD cohorts.[2,10] However, authors revealed that COVID-19 related coagulopathy poses a great burden on ACHD patients, as it dramatically increases mortality compared to patients that did not present a TE/bleeding event (33% vs 1.7%, $P < 0.0001$), with 4 of 10 of these deaths to be directly related to thromboembolism or major bleeding.[9] In addition, these patients experienced more frequently a new arrhythmic event and presented a severe COVID-19 infection (63% vs 5.2%, $P < 0.0001$) that required admission in intensive care unit (63% vs 4.2%, $P < 0.0001$), mechanical ventilation (50%) or extracorporeal membrane oxygenation (23%), and had a prolonged median hospital stay of 13 days. Overall, the majority of TE/bleeding events were noted among hospitalized ACHD patients.

In terms of baseline characteristics, patients who experienced either a thrombotic (n = 12), a bleeding

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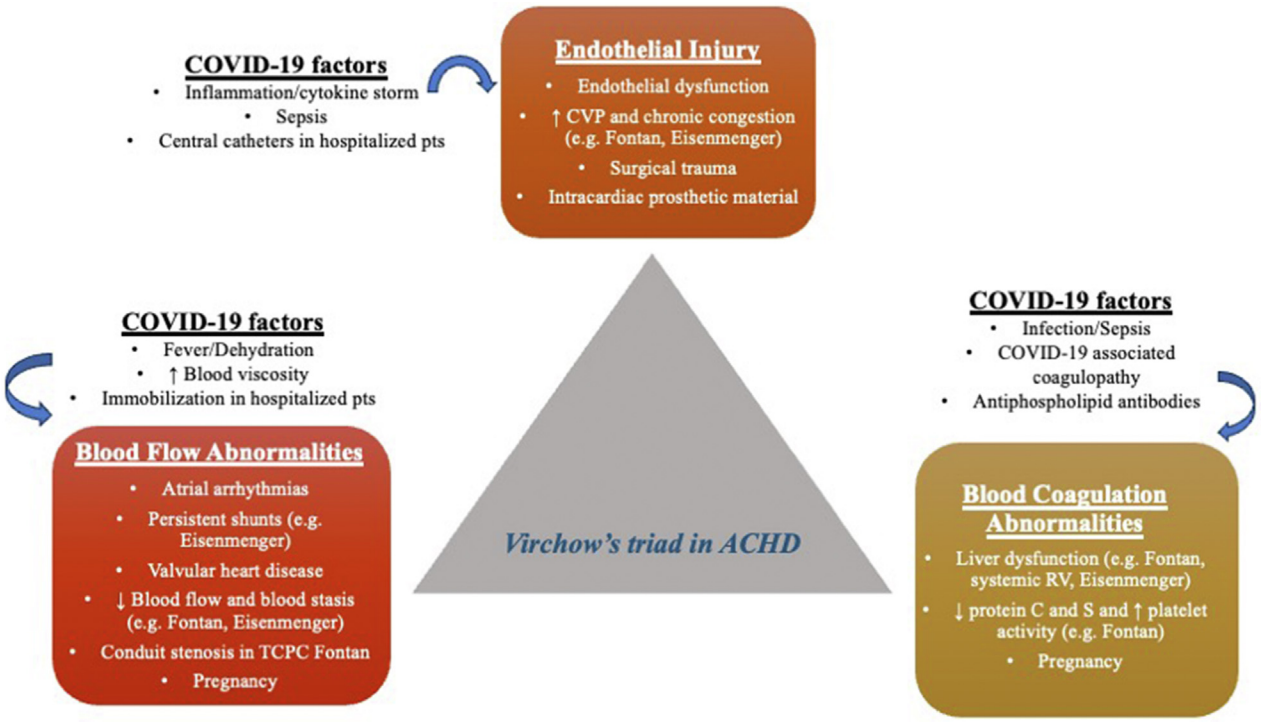
FIGURE 1 COVID-19 Related Thrombogenic Factors Impact on the Intrinsic Coagulopathy Status of Adults With Complex Congenital Heart Disease as Presented With the Virchow's Triad



ACHD = adult congenital heart disease; CVP = central venous pressure; RV = right ventricle; TCPC = total cavopulmonary connection.

(n = 12) or both events (n = 6) were in a more advanced physiological stage, presented a worse NYHA functional class and had a lower baseline arterial oxygen saturation prior to COVID-19 infection.[9] In addition, previous history of atrial arrhythmias and hospitalizations for heart failure, as well as preexisting coronary artery disease and the need for anticoagulation or antiplatelet therapy were all more common in patients who experienced a TE/bleeding event compared to those who did not, whereas anatomic complexity did not differ between the 2 groups.

Similarly, previous data from the same international, multicenter retrospective registry indicated that advanced physiological stage, cyanosis, and supplemental oxygen use as well as history of heart failure hospitalization and pulmonary arterial hypertension are associated with mortality in 1,044 ACHD patients with COVID-19, along with traditional cardiovascular risk factors (older age, male sex, obesity, diabetes, renal insufficiency).[11] Neither anatomic complexity nor significant valvular or ventricular dysfunction were related with mortality.[11] In the present study, among a variety of potential risk factors, previous use of anticoagulation, cardiac injury and severe COVID-19 infection emerged as independent predictors for TE/bleeding events in ACHD patients infected with COVID-19.[9]

Despite its retrospective design, possible referral bias and limited number of events, the study by Fusco et al[9] significantly enhances our knowledge about the impact of COVID-19 coagulation disorders in a wide spectrum of ACHD individuals and enables ACHD physicians to identify patients at higher risk for a TE/bleeding event and act proactively. This may be of particular interest for specific complex CHD categories, such as Eisenmenger syndrome or univentricular hearts palliated with the Fontan procedure. Although anatomic CHD complexity does not seem to predict the occurrence of a TE/bleeding event, COVID-19 infection severity or mortality, these patients are usually in a worse physiological stage, may be hypoxemic or cyanotic, have a low-flow circulation and experience more frequently arrhythmic events. Therefore, they present an inherent thrombotic propensity, which

encompasses all elements of Virchow's triad and thus, they often receive anticoagulation therapy, which further increases the risk of bleeding.[5,12-14] Therefore, it could be speculated that an additional coagulopathy burden due to COVID-19 would be devastating for these high-risk patients (**Figure 1**).

In conclusion, COVID-19 coagulation disorders can increase morbidity and mortality in infected ACHD patients. Early identification of patients at higher risk for coagulation complications and mortality is paramount in order to proactively treat this vulnerable population. Thus, a multidisciplinary approach with close cooperation between ACHD experts, internal medicine and intensive care unit physicians is required when managing ACHD individuals with a COVID-19 infection.[8]

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