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.

for the hand-eye coordination in minimally invasive surgery, which are deeply different from those required for traditional open operations.

The first procedures usually carried out using small animals are microvascular anastomoses. The end to side portocaval shunt, for instance, is a simple model, easy to learn and useful also in studying pathophysiologic alterations in some organs after diversion of the portal blood. The side to side portocaval shunt is another example, more complex because the portal vein and the inferior cava vein have to be adequately mobilized for anastomosing them without tension.[6]

In conclusion, many efforts should still be made to implement methods for the training of residents. In addition to curricula based on physical virtual simulation, experimental models could be used in this setting as well, having the double advantage of allowing the resident to acquire and develop practical skills, as well as giving them the opportunity to actively take part in a research activity.

REFERENCES

1. Schimpke SW, Larson BM, Veenstra BR, et al. Do one, do one, teach one: altering the dogma using simulation-based training to maximize efficiency of surgical resident education. J Am Coll Surg 2020;231:140–148.
2. Moglia A, Ferrari V, Morelli L, et al. Distribution of innate ability for surgery amongst medical students assessed by an advanced virtual reality surgical simulator. Surg Endosc 2014; 28:1830–1837.
3. Moglia A, Morelli L, Ferrari V, et al. Distribution of innate psychomotor skills recognized as important for surgical specialization in unconditioned medical undergraduates. Surg Endosc 2018;32:4087–4095.
4. Di Cataldo A, Li Destri G, Trombatore G, et al. Usefulness of microsurgery in the training of the general surgeon. Microsurgery 1998;18:446–448.
5. Di Cataldo A, Puleo S, Rodolico G. Three microsurgical courses in Catania. Microsurgery 1998;18:449–453.
6. Di Cataldo A, La Greca G, Rodolico M, et al. Experimental models in microsurgery. Microsurgery 1998;18:454–459.

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Fibrinolysis Shutdown in COVID-19-Infected Patients Can Result from Iron-Induced Stabilization of Fibril Clots

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Fibrinolysis shutdown in COVID-19 patients recently presented by Wright and colleagues[1] and commented on by Seheult and colleagues[2] unraveled the existence of an unusual mechanism of clot stabilization. Intriguingly, fibrinolysis shutdown is accompanied with markedly elevated D-dimer concentrations, a marker of hyperfibrinolysis. Stable clots persist despite activated fibrinolysis. This paradox can hopefully be explained, given that ferric ions (Fe^{3+}) induce formation of proteolytically insoluble parafibrin.[3] This iron-induced fibrin clot stabilization is mediated by hydroxyl radicals and seems to result from a cross-link of the fibril polymer. Therefore, in cytokine storm, when free iron is available, the regular balance between fibrosis and fibrinolysis is dynamically modulated by iron-mediated continuous catalytic clots stabilization.[3]

Although a role of iron homeostasis (FeH) is underestimated in COVID-19-related research, a "hyperferritinemic syndrome" is already a marker of deregulation of iron homeostasis in patients with COVID-19. If so, a disrupted FeH appears as a core of COVID-19-induced pathology. Cytokine storm is crucial in progression of the COVID-19-initiated pathology. It is accompanied by oxidative stress and erythrocyte destruction obviously, with subsequent dramatical influx of catalytically active iron into damaged tissue. After both local transferrin-binding capacity in physiological fluids and iron-sequestrating capacity of patrolling phagocytes are saturated, an excess of unbound catalytically active iron appears in the lungs. The systemic FeH is tightly regulated. The local FeH disturbance can hardly be monitored by serologic parameters. For this reason, there are just a few reports describing experimentally a deregulation of the local FeH in comparison with systemic FeH. For instance, levels of local hepcidin, a master regulator of FeH, increased in our animal model of the transplanted ascetic tumor in comparison with hepcidin concentrations in blood (T Sukhomlin, PhD, unpublished data, June 2013).

Apparently, the recently published effect of recombinant human erythropoietin administration for treatment of anemic patients infected with COVID-19[4] indirectly revealed a detrimental role of disrupted local FeH in COVID-19-induced pathology. The recombinant human erythropoietin administration possibly initiated temporal withdrawal of blood transferrin-bound iron for erythropoiesis from iron-overloaded inflamed organs. In addition to successful anticoagulant therapy, removal of an excess of free iron from the injured tissue could be beneficial in treatment of COVID-19 consequences.

REFERENCES

1. Wright FL, Vogler TO, Moore EE, et al. Fibrinolysis shutdown correlation with thromboembolic events in severe COVID-19 infection. J Am Coll Surg 2020;231:193–203.

2. Seheult JN, Seshadri A, Neal MD. Fibrinolysis shutdown and thrombosis in severe COVID-19. J Am Coll Surg 2020;231:203–204.
3. Pretorius E, Vermeulen N, Bester J, et al. A novel method for assessing the role of iron and its functional chelation in fibrin fibril formation: the use of scanning electron microscopy. Toxicol Mech Methods 2013;23:352–259.
4. Hadadi A, Mortezazadeh M, Kolahdouzan K, Alavian G. Does recombinant human erythropoietin administration in critically ill COVID-19 patients have miraculous therapeutic effects? J Med Virol 2020;92:915–918.

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Usefulness of Combining D-Dimers with Thromboelastography

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Wright and colleagues[1] have elegantly shown that fibrinolytic shutdown is hugely contributory to the hypercoagulability in COVID-19. In addition, they demonstrate a very important clinical point that combining D-dimers with thromboelastography can predict the need for dialysis in patients with COVID-19. Several other important considerations can be derived from this study. First, it is well-known that D-dimers are an inflammatory marker and can elevate several inflammatory diseases, including COVID-19, even in the absence of thrombosis.[2] The report by Wright and colleagues would suggest the addition of thromboelastography to D-dimer would help in understanding how much of the D-dimers are from clot breakdown and how much are nonthrombotic D-dimers. Second, because D-dimers are markers of clot breakdown, their elevation in conjunction with fibrinolysis shutdown would mean some of these D-dimers are not created from plasmin action on crosslinked fibrin. It is possible that these D-dimers are created in the lungs from bronchoalveolar-specific clot breakdown, which might not be detected by thromboelastography on peripheral blood.[3] It is also possible that a proportion of D-dimers are not generated by clot breakdown at all, but by the action of plasmin on the extravascular fibrin. Lung exudates seen in acute lung injury could constitute large amounts of fibrinogen and thrombin leaked from the intravascular space along with other plasma proteins.[4] Plasmin breakdown of fibrin formed from these large amounts of fibrinogen could be another cause of these nonthrombotic D-dimers. In the case of extravascular D-dimers, these fibrinolytic markers would signify the intense intrapulmonary inflammatory reaction and could be considered a marker of ongoing or increasing inflammation. Recognizing the roles of this intense inflammation in combination with microvascular thrombi for renal impairment is crucial. Anticoagulation could only prevent the thrombotic component of this contribution and anti-inflammatory strategies might also be required to minimize the renal damage.[5] Of course, the dual anticoagulant and anti-inflammatory properties of heparin might be helpful in this scenario, but possibly only in the early stages before marked inflammation sets in. Future studies would complement this current article by examining the timing of marked D-dimer elevation and fibrinolysis shutdown by viscoelastic testing to better understand the thromboinflammatory concept.

REFERENCES

1. Wright FL, Vogler TO, Moore EE, et al. Fibrinolysis shutdown correlates to thromboembolic events in severe COVID-19 infection. J Am Coll Surg 2020;231:193–203.e1.
2. Favresse J, Lippi G, Roy PM, et al. D-dimer: preanalytical, analytical, postanalytical variables, and clinical applications. Crit Rev Clin Lab Sci 2018;55:548–577.
3. Levi M, Schultz MJ, Rijneveld AW, van der Poll T. Bronchoalveolar coagulation and fibrinolysis in endotoxemia and pneumonia. Crit Care Med 2003;31[Suppl]:S238–S242.
4. Wagers SS, Norton RJ, Rinaldi LM, et al. Extravascular fibrin, plasminogen activator, plasminogen activator inhibitors, and airway hyperresponsiveness. J Clin Invest 2004;114:104–111.
5. Fani F, Regolisti G, Delsante M, et al. Recent advances in the pathogenetic mechanisms of sepsis-associated acute kidney injury. J Nephrol 2018;31:351–359.

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Untangling the Reasons Surgeons Choose to Leave Clinical Practice, including Retirement

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