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Anticoagulation management associated with extracorporeal circulation

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The use of extracorporeal circulation requires anticoagulation to maintain blood fluidity throughout the circuit, and to prevent thrombotic complications. Additionally, adequate suppression of hemostatic activation avoids the unnecessary consumption of coagulation factors caused by the contact of blood with foreign surfaces. Cardiopulmonary bypass represents the greatest challenge in this regard, necessitating profound levels of anticoagulation during its conduct, but also quick, efficient reversal of this state once the surgical procedure is completed. Although extracorporeal circulation has been around for more than half a century, many questions remain regarding how to best achieve anticoagulation for it. Although unfractionated heparin is the predominant agent used for cardiopulmonary bypass, the amount required and how best to monitor its effects are still unresolved. This review discusses the use of heparin, novel anticoagulants, and the monitoring of anticoagulation during the conduct of cardiopulmonary bypass.

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The development of anticoagulation for cardiopulmonary bypass

While the birth of cardiopulmonary bypass (CPB) is widely celebrated as 6 May 1953, when Dr. John Gibbon successfully utilized it during the closure of an atrial septal defect, it is less appreciated that extracorporeal circulation for organs was actually conceived >100 years earlier by the French physiologist Julien-Jean Cesar le Gallois [1]. One of the greatest obstacles faced by le Gallois and other early developers of CPB was the profound activation of the coagulation system, resulting in clotting of circuits and thrombosis of vessels. Defibrinated blood was used in conjunction with bubble-type oxygenators as early as 1856, but reliable systemic anticoagulation remained elusive [2]. It was not until the discovery of heparin by Howell and McLean in 1916, and really only following the development of high-yield manufacturing processes in the late 1930s, that anticoagulation for CPB became feasible [3].

Early protocols for heparin administration were simply weight-based with little attempt at monitoring its effects. In 1957, the Mayo Clinic described "prevention of the coagulation of blood" for the Gibbon-type pump oxygenator, prescribing 3 mg of heparin (i.e., 300 units) per kilogram of patient bodyweight [4]. The activated clotting time (ACT) of whole blood was reported by Hattersley in 1966 [5], and this eventually led to a practical point-of-care testing that could be imported into the operating room for monitoring the effects of heparin. Bull et al. popularized the concept of the "safe zone" for anticoagulation during CPB in the mid-1970s, defining this as an ACT between 300 and 600 s [6].

It is intuitively evident that clot formation in CPB circuits can lead to devastating complications, but preventing thrombi is actually only one of the goals of anticoagulation. A variety of mechanisms lead to thrombin production during CPB, which can activate and consume critical hemostatic components including platelets, fibrinogen, and other coagulation factors [7]. Somewhat paradoxically, inadequate anticoagulation on CPB can lead to a profound coagulopathy, likely due to disseminated intravascular coagulation (DIC), upon its termination. This review attempts to summarize the knowledge gained over the past 40 years, and to guide clinicians with respect to the practice of anticoagulation for adults on CPB.

Anticoagulation agents

Despite its age, which is older than the US Food and Drug Administration (FDA), heparin remains the anticoagulant of choice for extracorporeal circulation. It can achieve profound levels of anticoagulation, is inexpensive, and it has a readily available antidote in protamine. Unfortunately, it also has significant limitations that have led to the search for alternate agents. Clinicians today are faced with an increasing array of choices for providing anticoagulation for CPB. While most are reserved for situations where heparin cannot be used, it is important to understand their potential benefits and limitations. Table 1 summarizes the dosing information of the below agents that have been used in the setting of CPB.

Unfractionated heparin

Unfractionated heparin (UFH) is a heterogenous mixture of sulfated polysaccharides prepared from animal tissues. The primary source has changed over the years from canine liver to bovine lung, and it is now predominantly porcine intestine. The extraction and purification processes result in a mixture of polysaccharide chains of 5–30 kDa in weight, of which 20–50% contain the specific pentasaccharide-binding site for the protein antithrombin (AT) [8]. The primary mechanism of UFH's anticoagulant effect is largely indirect, in that it accelerates AT's endogenous inhibition of factor IIa (thrombin) and factor Xa by >1000-fold each. The ratio of thrombin to Xa inhibition for UFH is assumed to be 1:1. Importantly, the neutralization of thrombin by AT requires heparin chains of higher molecular weight, containing at least 18 saccharide units. Low molecular weight heparins (LMWHs), provided they contain the specific pentasaccharide sequence, can still bind to AT and accelerate its inhibition of Xa, but inhibition of thrombin is severely reduced [8]. Factors IXa, XIa, and XIIa are also inactivated by the heparin–AT complex, although to a much lesser degree [9]. Once AT binds to the coagulation factor, the heparin molecule is released and available to bind to other targets.