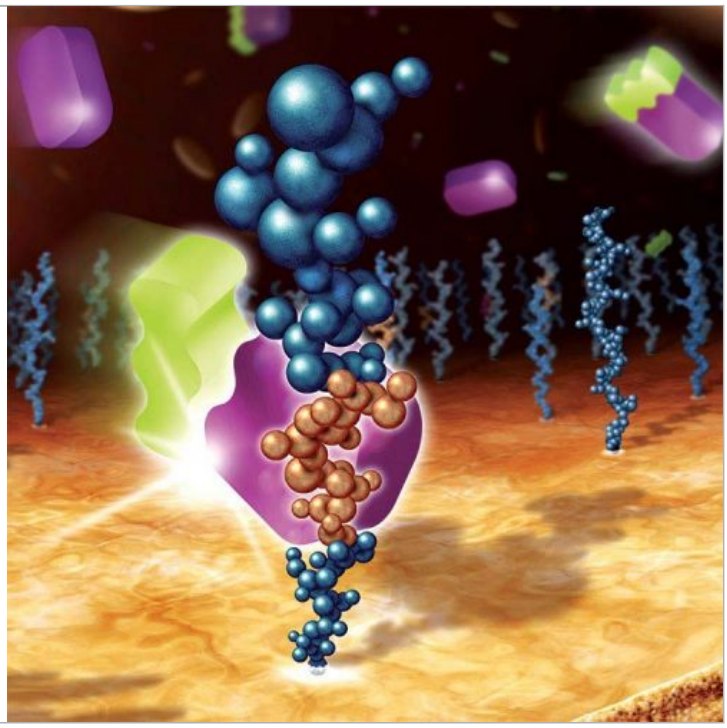
⚠ Indications, Safety, and Warnings

HEALTHCARE PROFESSIONALS

Cortiva BioActive Surface

Biocompatible Surface for Cardiopulmonary Bypass Devices



OVERVIEW

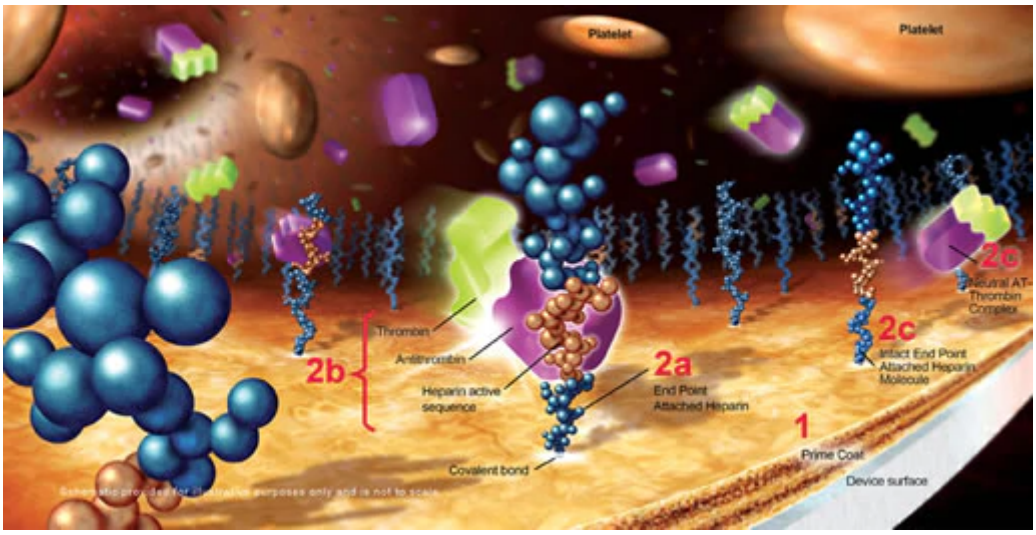
The bioactive coating marketed by Medtronic under the name Cortiva BioActive Surface is the most researched biosurface for today's extracorporeal circulation technologies, with extensive publication of clinical and scientific evidence in peer-reviewed cardiovascular surgery, perfusion, and scientific literature.

THROMBORESISTANCE AND ENHANCED BLOOD COMPATIBILITY

Cortiva BioActive Surface is a durable, non-leaching End Point Attached heparin coating technology that enhances blood compatibility and provides thromboresistant blood-contacting surfaces for cardiopulmonary bypass circuit devices. This heparin coating has the largest body of peer-reviewed clinical and scientific evidence of any biocompatible surface used for cardiopulmonary bypass devices today. From paediatric patients to adults, Cortiva BioActive Surface is an

important component of routine as well as complex extracorporeal circulation procedures.

END POINT ATTACHED HEPARIN TECHNOLOGY



1. Prime Coat

Alternating layers of cationic and anionic polymers are deposited on the device surface via electrostatic adsorption to provide a consistent substrate that allows the Cortiva BioActive Surface to be applied to a variety of device materials, including plastics and metals.

2a. End Point Attachment Bonding Process

Heparin is bonded to the surface using End Point Attachment. End Point Attached heparin molecules are oriented to the blood in a manner similar to that of heparan sulfate naturally found on the vascular endothelium. The heparin molecules protrude into the blood, allowing their active sequences to interact with the blood. End Point Attachment of heparin results in a strong, covalent bond so that heparin does not leach from the surface during extracorporeal circulation in the presence of blood or albumin.

2b. Potent Surface Anticoagulant Activity

The End Point Attached heparin active sequence binds to antithrombin (AT) in the blood, resulting in a heparin-AT complex that has a much higher affinity for blood coagulation factors than AT alone. Attachment of activated blood coagulation factors to AT forms harmless inactive complexes that are no longer available to participate in or trigger other events in the coagulation cascade. For example, the activated blood coagulation factor II (thrombin) binds to the heparin-AT complex and subsequently becomes inactivated.

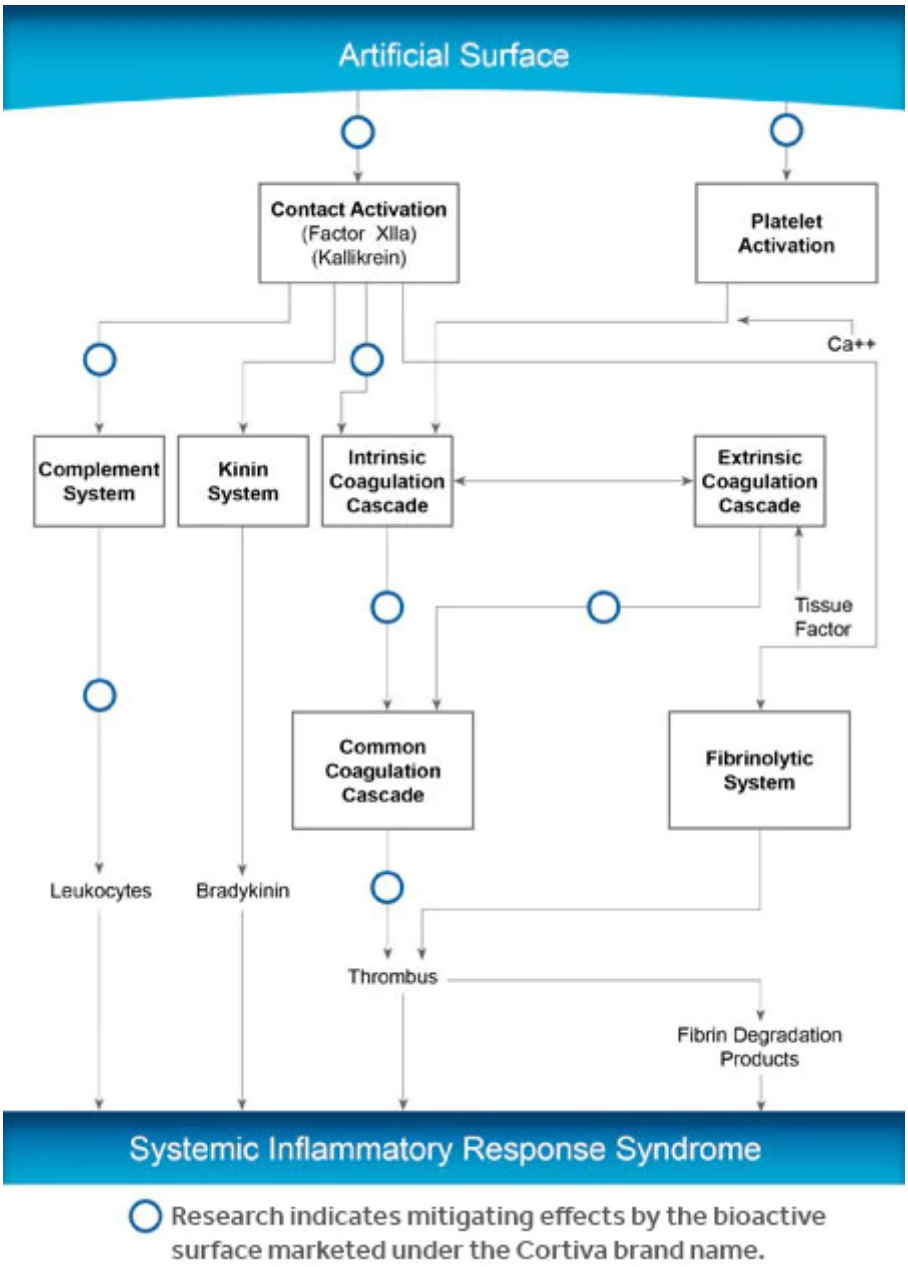
2c. Intact End Point Attached Heparin Molecule

The End Point Attached heparin molecule is not consumed by this cycle and remains bonded, intact, to the material surface. Its anticoagulant active sequence is then free to attach to another AT molecule.

2c. Neutral AT-Thrombin Complex

AT-coagulation factor complexes are then released from the immobilised heparin and are swept away from the surface by the flowing blood. These complexes are eventually metabolised by the body.

EXTENSIVE PEER-REVIEWED CLINICAL AND SCIENTIFIC EVIDENCE



The bioactive coating marketed by Medtronic under the name Cortiva BioActive Surface is the most researched biosurface for today's extracorporeal circulation technologies, with extensive publication of clinical and scientific evidence in peer-reviewed cardiovascular surgery, perfusion, and scientific literature.

- Less blood product use[1,2,3,4,5,6,7]
- Less perioperative blood loss[5,6,7,8,9,10,11,12]
- Shorter ventilator time[3,6,9,13,14]
- Shorter hospital length of stay[2,3,9]
- Less postoperative body temperature rise[9,15]
- Significantly greater urine output during CPB[13]
- Lower costs, as related to improved clinical outcomes[3]
- Less negative impact on the body's defense systems, including the:
  - contact system[16,17,18,19,20,21]
  - coagulation system[11,17,22,23,24,25,26,27,28,29,30,31]
  - fibrinolytic system[6,23,32,33]
  - complement system[10,12,14,22,29,33,34,35,36,37,38,39,40]
  - cytokine proteins[14,26,33,35,39,40]
- Reduced impact on the blood's formed elements, including:
  - platelets[10,17,26,29,30,37,39,41]
  - red blood cells[11,16,20,25,32,35,42]
  - leukocytes[14,20,26,29,30,33,36,37,38]

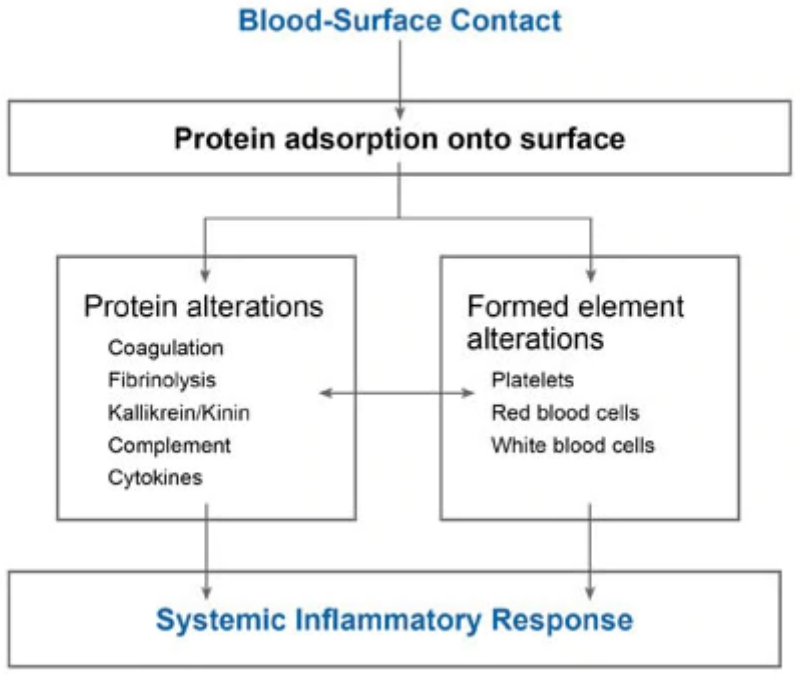
Note: Citations with bold font represent clinical studies. Citations with standard font represent experimental *in vitro* and *in vivo* studies.

WHY USE BIOCOMPATIBLE SURFACES FOR EXTRACORPOREAL CIRCULATION CIRCUITS?

Blood is naturally compatible with vascular endothelium, not artificial surfaces.

- Blood is compatible with the healthy vascular endothelium, a single layer of cells that lines all blood vessels and the heart.
- The endothelium plays an active biological role in maintaining homeostasis, or a balance, among the various body defense systems in a manner that simultaneously provides a state of readiness and avoids the trigger of adverse responses.[43, 44]
- The blood-contacting surfaces of endothelial cells are highly negatively charged, a characteristic that may repel the negatively charged platelets and be important in limiting the haemostatic reaction.[45]

Blood recognises the extracorporeal circuit surfaces as “foreign”, triggering coagulation and inflammatory events that may lead to adverse patient outcomes.



Responses to Blood-Material Contact

- Within seconds of blood exposure to artificial, non-endothelial surfaces, there is a rapid adsorption of proteins from the blood onto the surface of the foreign material.[46]
- Adsorption onto a surface may result in protein denaturation, such as the denaturation of adsorbed fibrinogen, and ultimately lead to activation of the plasma proteolytic systems.[43] Subsequent events, including cell adhesion, are mediated by the adsorbed protein layer.[43]
- The blood's formed elements and other specific protein groups in the blood that are associated with the body's defense systems may then interact with the material and its new protein layer.[43, 44]
- Ultimately, the biological reactions associated with the defense systems may affect the heart, lungs, brain and other organs, causing conditions that have been described as the "systemic inflammatory response syndrome." [47]

Biocompatible surfaces for Medtronic extracorporeal circulation technologies mimic critical characteristics of the vascular endothelium.

- These coatings mitigate the foreign body response that occurs when blood comes in contact with non-endothelial surfaces.
- Around the world, leading cardiovascular surgery teams adopt coatings surfaces offered by Medtronic as a critical component of comprehensive, multi-modal strategies to achieve the best possible outcomes for their patients undergoing extracorporeal circulation.

Warnings: A strict anticoagulation protocol should be followed and anticoagulation should be routinely monitored during all procedures. The benefits of extracorporeal support must be weighed against the risk of systematic anticoagulation and must be assessed by the prescribing physician.

Caution: For a complete listing of indications, contraindications, precautions and warnings, please refer to the Instructions for Use which accompany each product.

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PROTECT THE CIRCUIT, PROTECT THE PATIENT. [1, 8, 22, 35]

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