Improving health care quality for patients undergoing extracorporeal circulation procedures is a high priority today as patient outcomes measures are increasingly, and often publicly, scrutinized.

Today's leading cardiovascular surgery teams strategically apply teamwork, techniques and technologies to achieve the best possible outcomes for their patients undergoing extracorporeal circulation. Around the world, Carmeda® BioActive Surface is an important component of these comprehensive strategies.

Blood is meant to contact the healthy vascular endothelium that lines the blood vessels and heart, not artificial surfaces. The activation of the blood’s formed and unformed elements, which occurs when blood contacts the extracorporeal circuit’s artificial surfaces, is associated with an induction of two highly interconnected events: coagulation and inflammation. These events may affect the body’s organ systems and compromise clinical outcomes.

The important role of Carmeda® BioActive Surface is to provide thromboresistance and biocompatibility by reducing the impact of blood contact with the circuit’s artificial surfaces. A large body of published clinical and scientific evidence reports the beneficial impact of Carmeda® BioActive Surface on the body’s defense systems and on clinical outcomes for both adult and pediatric patients.

*Manufactured under license from Carmeda AB, Sweden. Carmeda is a registered trademark of Carmeda AB.

This compendium of clinical and scientific information describes the role of Carmeda® BioActive Surface during extracorporeal circulation procedures, reviews the evolution of heparin biosurface technology, highlights Carmeda® BioActive Surface’s technological characteristics and theory of function, and summarizes the large body of published supporting clinical and scientific evidence for this End Point Attached heparin technology.
Today's Strategies to Reduce Extracorporeal Circulation-related Morbidity: The Role of Carmeda® BioActive Surface

Extracorporeal circulation procedures help save lives and enhance the quality of life. They can also make patients ill.

Carmeda® BioActive Surface was developed to minimize one contributor to extracorporeal circulation-related morbidity: the contact-initiated activation of the blood’s coagulation system and the subsequent activation of platelets that occurs when blood comes in contact with the artificial materials lining extracorporeal circuits. Activation of the blood’s formed and unformed elements is associated with an inflammatory response that may affect the body’s organ systems, disturb blood coagulation processes and compromise clinical outcomes.

Carmeda® BioActive Surface provides thromboresistance and biocompatibility to extracorporeal circuit surfaces.

For pediatric patients to adults, Carmeda® BioActive Surface bonded circuits are used for routine as well as complex procedures requiring extracorporeal circulation.

Carmeda® BioActive Surface is a critical component of comprehensive strategies to reduce extracorporeal circulation-related morbidity.

Besides blood-surface interactions, there are several other potential contributors to extracorporeal circulation-related morbidity. Therefore, leading clinical teams strategically apply teamwork, techniques and technologies that carefully consider the many surface-, flow-, and blood-related issues that may impact patient outcomes (Figure 1). Heparin biocompatible surfaces are an important component of these comprehensive strategies for achieving the best possible outcomes for patients undergoing extracorporeal circulation (Table 1).

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**Table 1**

<table>
<thead>
<tr>
<th>Strategies for Reducing Extracorporeal Circulation-Related Morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Published evidence suggests that extracorporeal circulation-related morbidity may be reduced by:</td>
</tr>
<tr>
<td>- Using a heparin biocompatible surface for blood-contacting areas on the circuit</td>
</tr>
<tr>
<td>- Preventing excessive hemodilution</td>
</tr>
<tr>
<td>- Reducing shear, stasis and turbulence</td>
</tr>
<tr>
<td>- Using closed-to-air systems and other techniques and technologies to limit air-blood interface</td>
</tr>
<tr>
<td>- Minimizing manipulation of the aorta</td>
</tr>
<tr>
<td>- Avoiding direct reinfusion of unprocessed cardiotomy suction blood</td>
</tr>
<tr>
<td>- Providing precise, patient-specific hemostasis management</td>
</tr>
</tbody>
</table>

---

**Figure 1**

Teamwork – Technique – Technology Strategies for Improving Extracorporeal Circulation Outcomes

- Minimize:
  - Shear
  - Stasis
  - Turbulence

- Prevent excessive hemodilution
- Prevent emboli
- Avoid direct reinfusion of cardiotomy suction blood
- Optimal pharmacological management
- Precise, patient-specific hemostasis management

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Carmeda® BioActive Surface is an important component of comprehensive strategies for reducing extracorporeal circulation-related morbidity.
Clinical applications

- Extracorporeal circulation procedures for patients of all ages and sizes, pediatric to adult

Materials bonded

- Plastic and metal materials that line the blood-contacting surfaces of the extracorporeal circuit components

Extracorporeal technologies bonded

- Oxygenators
- Centrifugal blood pumps
- Cardioplegia delivery systems
- Arterial filters
- Reservoirs
- Flow probes
- O₂ saturation cells
- Resting Heart® System
- Custom tubing sets
- Closed chest support system
- Hemodynamic support system
- Cannulae
- Cannulae adapters

Clinical and scientific findings

Carmeda® BioActive Surface is the most extensively 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, including:

- Less blood product use²³,²⁹,³⁰,³¹,³²
- Less perioperative blood loss⁶,30,31,32,33,34,35,36
- Shorter ventilator time²,31,33,37,38 and reduced post-operative peak airway pressures³⁹
- Shorter ICU³,⁴ and hospital²³,³¹ length of stay
- Less postoperative body temperature rise³³,⁴⁰
- Fewer postoperative neurocognitive deficits⁵,³³,⁴¹
- Significantly greater urine output during CPB³¹,³⁷
- Lower costs, as related to improved clinical outcomes³
- Less negative impact on the body’s defense systems, including the:
  - contact system⁴²,⁴³,⁴⁴,⁴⁵,⁴⁶,⁴⁷
  - coagulation system⁵,³⁵,³⁴,⁴⁸,⁴⁹,⁵⁰,⁵¹,⁵²,⁵³,⁵⁴,⁵⁵,⁵⁶
  - fibrinolytic system⁴,⁵,⁴⁸,⁵⁸
  - complement system⁴,³⁵,³⁴,³⁶,³⁸,³⁹,⁵⁰,⁵⁴,⁵⁹,⁶⁰,⁶¹,⁶²,⁶³,⁶⁴
  - cytokine proteins⁴,³⁸,³⁹,⁵¹,⁶⁰,⁶⁴
- Reduced impact on the blood’s formed elements, including:
  - platelets³⁴,⁴³,⁵¹,⁵⁴,⁵⁵,⁶²,⁶⁴,⁶⁵
  - red blood cells³¹,³⁵,⁴⁶,⁵⁰,⁵⁷,⁶⁶
  - leukocytes³⁸,⁴⁶,⁵¹,⁵⁴,⁵⁵,⁶¹,⁶²,⁶³

Carmeda® BioActive Surface Mimics Critical Characteristics of the Vascular Endothelium

Heparin

- High degree of bioactivity is consistently delivered, due to the unique Carmeda® BioActive Surface chemistry and its sophisticated manufacturing process.
- End Point Attached heparin bonding process assures that the heparin molecules’ active binding sites remain free to participate in biological reactions with the blood components.
- Durable, non-leaching heparin surface that does not wash off is provided by the strong covalent bonding process used to immobilize the End Point Attached heparin on the device surface.

Negative charge

- Similar to the negative charge of the vascular endothelium, the heparin in Carmeda® BioActive Surface is negatively charged.

Hydrophilicity

- Hydrophilic, or “water loving,” characteristics are provided by Carmeda® BioActive Surface’s heparin and priming layer.
- Hydrophilic surfaces adsorb less blood protein compared to hydrophobic, or “water hating,” surfaces; this protein adsorption is also more readily reversible⁶⁷,⁶⁸,⁶⁹
Blood is naturally compatible with vascular endothelium, not artificial circuits.

Healthy vascular endothelium: The ultimate biocompatible surface

Inside the human body, blood is compatible with the healthy vascular endothelium. In contrast, outside the body, blood is not compatible with artificial surfaces, including the materials that line the blood pathway of extracorporeal circuits and the air found in open reservoir systems.

The endothelium is a monolayer of cells that lines all blood vessels and the heart. Complex biologic mechanisms within the vascular endothelium maintain blood within the vessels without causing thrombosis or clotting (coagulation). The healthy, uninjured endothelium layer produces inhibitors of blood coagulation and platelet aggregation. Vascular endothelium modulates vascular tone and permeability and provides a protective envelope that separates hemostatic blood components from reactive subendothelial structures that could lead to platelet adhesion and activation of the coagulation system. Endothelial cells are highly negatively charged, a characteristic that may repel the negatively charged platelets and be important in limiting the hemostatic reaction.

The endothelium plays an active biological role in maintaining homeostasis, or a balance, among the various body defense systems in a manner that provides a state of readiness and simultaneously avoids the trigger of adverse responses. These defense systems initiate hemostasis to maintain vessel integrity, stimulate fibrinolysis to dispose of fibrin and consequently dissolve clots, attack foreign bodies, activate the immune systems, and perform other roles to maintain or restore the balance among the defense systems.

Blood contact with artificial surfaces may trigger an inflammatory response that can lead to patient morbidity.

When foreign material comes in contact with a body tissue, the body recognizes it as “foreign” and initiates an inflammatory response. The general response that occurs when blood tissue contacts an artificial material is depicted in Figure 4.

The blood is a fluid tissue with a composition that includes formed elements, such as platelets and various types of blood cells (red blood cells or “erythrocytes;” white blood cells or “leukocytes”), and unformed soluble elements, such as the plasma proteins. During extracorporeal circulation, activation of the blood’s formed and unformed elements, due to contact with the circuit’s artificial surfaces, initiates a number of the biological pathways and elements involved in the inflammatory response, including the coagulation, fibrinolysis, kallikrein and complement activation cascades as well as the cytokine proteins (Table 2). Within seconds of blood exposure to these artificial, non-endothelial surfaces, there is rapid adsorption of proteins, such as the coagulation protein fibrinogen, from the blood onto the surface of the material. The final composition of this very thin protein layer is specific for each type of material and is affected by many factors, including the chemical and physical nature of the material, the concentrations of various proteins in the blood and the affinities of these proteins for a specific surface. For example, hydrophilic, or “water loving” surfaces adsorb less blood protein compared to hydrophobic, or “water hating,” surfaces; hydrophilic protein adsorption is more readily reversible.
Adsorption onto a surface may result in protein denaturation, such as the denaturation of adsorbed fibrinogen, and lead to activation of the plasma proteolytic systems. Subsequent events, including cell adhesion, are mediated by the adsorbed protein layer.

Following the general protein response, blood cells and other specific protein groups in the blood that are associated with the body’s defense systems may interact with the material and its new protein layer (Tables 2 and 3).

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 “post-perfusion syndrome” or the “systemic inflammatory response syndrome” (SIRS) or the “whole body inflammatory response.” Clinical manifestations of SIRS are highlighted in Table 4.

**End Point Attached heparin mimics critical characteristics of the vascular endothelium.**

Due to the vascular endothelium’s active role in maintaining the checks and balances of the body’s defense systems, the harmful biologic reactions that are generated during extracorporeal circulation do not occur when normal blood circulates through intact blood vessels lined by healthy endothelial cells.

Heparan sulfate, a proteoglycan that is structurally and functionally similar to the anticoagulant heparin, is naturally found on the endothelial cell surface of the vascular wall. Its structure consists of a central protein core to which polysaccharide chains are bound.

Heparan sulfate molecules are linked to endothelial cells in a manner that exposes the polysaccharide chains, making the chains highly accessible to protein molecules in the blood.

Particular binding sequences on the heparan sulfate molecules bind with proteins in the blood. Heparan sulfate activates plasma serine protease antithrombin (AT), a type of blood protein, catalyzing the inhibition of thrombin and factor Xa, two other types of blood proteins, or enzymes, that play a role in the blood coagulation process.

End Point Attached heparin mimics the orientation of the heparan sulfate molecule on the vascular endothelium so the surface-immobilized heparin’s active sequence is exposed and available to interact with blood elements. In other heparin bonding methods, the active sequence often becomes part of the bond between the heparin molecule and the surface, resulting in unavailability of the active sequence for interactions with blood.

The evolution of heparin biosurfaces and the development of End Point Attached heparin technology will be discussed in greater detail in the following section. Specific information on the manner in which Carmeda® BioActive Surface mimics critical characteristics of the vascular endothelium can be found on page 9.

### Table 4

**Systemic Inflammatory Response Syndrome: Potential Clinical Manifestations**

<table>
<thead>
<tr>
<th>Organ dysfunction:</th>
<th>Increased susceptibility to infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary</td>
<td>Capillary permeability</td>
</tr>
<tr>
<td>Renal</td>
<td>Transcapillary plasma loss</td>
</tr>
<tr>
<td>Gut</td>
<td>Increased interstitial fluid</td>
</tr>
<tr>
<td>Central nervous system</td>
<td></td>
</tr>
<tr>
<td>Cardiac</td>
<td></td>
</tr>
<tr>
<td>Coagulation disorders</td>
<td></td>
</tr>
<tr>
<td>Leukocytosis</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 5**

Carmeda® BioActive Surface: Impact on Surface Deposition of Blood Elements

Scanning electron micrographs of oxygenator fiber surfaces after one hour of in vitro circulation in a closed system using heparinized, diluted human blood (100x magnification)
All heparin biosurfaces are not created equal: the history of End Point Attached heparin.

Carmeda® BioActive Surface End Point Attached heparin was developed to overcome the limitations of earlier heparin binding methods, providing a durable heparin biosurface while preserving the key structural and biological relationships of heparin essential to its activity.

Heparin and heparin biosurfaces - background

Anticoagulation using unfractionated heparin has made cardiopulmonary bypass possible since John Gibbon’s first successful procedure more than five decades ago. The concept of coating blood contact surfaces with heparin first originated because of the molecule’s anticoagulant properties. Attempts to heparinize surfaces eventually led to development of the End Point Attached heparin method of bonding heparin to the inner surface of extracorporeal circuits, as is used with Carmeda® BioActive Surface.

Heparin is a polysaccharide that is naturally found in mast cells of connective tissue. Although it has anticoagulant properties, heparin is not naturally found in the circulation, unlike the similarly structured heparan sulfate molecules attached to endothelial cells lining the vascular walls. Commercial heparin preparations are isolated from animal tissues such as porcine intestinal mucosa.

Heparin’s anticoagulant effect is attributed to its ability to bind to antithrombin (AT), a protease inhibitor found in the plasma. AT inactivates thrombin and enzymes responsible for the generation of thrombin. When heparin binds to AT, the AT molecule configuration is altered, increasing the rate of enzyme-inhibitor complex formation by a factor of 1,000 or more. The enzyme-inhibitor complex then detaches from the heparin molecule, leaving the heparin molecule available to interact with another AT molecule. Heparin is not consumed in this process, but rather acts as a catalyst.

Heparin biosurfaces for extracorporeal circulation have evolved using three basic types of heparin attachment:

- Ionic bonding
- Covalent bonding
- End Point Attachment

Ionically bonded heparin: an early attempt at heparin immobilization

Ionic bonding processes were developed during earlier attempts at surface immobilization of heparin. An ionic bond is an electrical attraction between two oppositely charged atoms. The formation of an ionic bond requires that one substance give up electrons to the other substance, leaving one negatively-charged and one positively-charged ion. In the case of heparin coating and the cardiopulmonary bypass (CPB) circuit surface, the CPB circuit surface gives up electrons to the coating and the two attract to form an ionic bond (Figure 6).

The ionic bond leaves the anticoagulant active sequence of the heparin free. However, an ionic bond, because it is between two essentially unstable ions, is not very stable, and the coating tends to wash off when blood flows through the CPB circuit. Later methods of ionic bonding attempted to stabilize the relatively weak bond of ionically bound heparin biosurfaces by using surfactants or by incorporating crosslinking reagents such as glutaraldehyde. While this combination was better, leaching continued to be an issue when the coating came into contact with blood, because proteins such as albumin break the ionic bond, releasing heparin into the bloodstream. Heparin leaching can result in increased levels of circulating heparin in the systemic circulation. Also, heparin leached into the blood is no longer available on the device surface to provide thromboresistance and biocompatibility.

Figure 6: Ionically Bonded Heparin: a Schematic

Ionically bonded heparin is less stable and tends to wash off when blood flows through the CPB Circuit.
Covalently bonded heparin: improved stability but limited bioavailability of immobilized heparin

Covalent bonding techniques were later developed to overcome limitations of ionic bonding, such as instability and heparin leaching. A covalent bond is created when two atoms share one or more pairs of bonding electrons. Each atom donates the electrons for one half of the pair(s).

Atoms in covalent bonds are more stable than ionic bonds. Covalent bonds are therefore stronger than ionic bonds and prevent heparin leaching from the coating on CPB surfaces.

An issue with most covalent bonding processes is that the orientation of the heparin molecule is not controlled. Consequently, the heparin molecule’s anticoagulant active sequence may become part of the bond between the heparin molecule and the surface, therefore becoming unavailable to interact with the blood circulating through the CPB circuit (Figure 7). In addition, the heparin’s chain conformation may become restricted so that it cannot attain the proper conformation required to bond with blood proteins. The End Point Attached method of heparin bonding was subsequently developed to address this issue.

End Point Attached heparin: a breakthrough in bioavailability and durability of surface immobilized heparin

As heparin surface immobilization technology evolved, the importance of preserving specific binding sites on the heparin complex and keeping the sites available to achieve maximum reactivity became evident. For example, it became known that the active binding site on heparin for binding antithrombin is a specific sequence of five saccharide residues.

Larm et al.86 first described a method of attaching heparin in which reactive aldehyde groups on heparin molecules were covalently bonded to amine groups on a prepared material surface. With this process, the aldehyde group on each heparin molecule is covalently bound to the prepared artificial surface (End Point Attached) and the remainder of the molecule, including the active binding sequence, is free to interact with the blood and not involved in the surface attachment mechanism (Figure 8). This leaves the active binding sequences available for biological reactions during extracorporeal circulation. Because its End Point Attachment technique incorporates a covalent bond, the heparin surface immobilization in Carmeda® BioActive Surface is stable, durable and does not wash off during extracorporeal circulation.

End Point Attached heparin bonding technology provides a surface that is “bioactive” (Table 5) to reduce coagulation and inflammation responses due to the blood-material surface interaction described on pages 5–6. It mimics critical characteristics of the vascular endothelium and its active role, discussed in greater detail beginning on page 9.

Medtronic has exclusive licenses to Carmeda® BioActive Surface Endpoint Attached heparin technology for extracorporeal circulation applications.

Medtronic has exclusive licenses for use of Carmeda® BioActive Surfaces for extracorporeal membrane oxygenation systems and additional license rights to certain other applications from Carmeda® AB, Sweden (www.carmeda.com), the developer of Carmeda® BioActive Surface.

Carmeda® BioActive Surface also has an extensive history of use across several additional medical applications®:® offered by other manufacturers, including vascular grafts, ventricular assist devices, stents, intraocular lenses and diagnostic devices.87

** Note: Certain device applications may not be available in the United States.
Mimicking critical characteristics of the vascular endothelium with Carmeda® BioActive Surface

Carmeda® BioActive Surface provides thromboresistance and biocompatibility for the blood-contacting surfaces of extracorporeal circulation circuits to address the foreign body response that is initiated when blood comes in contact with non-endothelial surfaces. Its End Point Attached heparin technology mimics critical characteristics of the vascular endothelium and its active role.

Heparin’s antithrombin (AT) binding sequence is critical for biological interactions with the blood.

- Heparin is a heterogeneous, heavily sulfated polysaccharide compound that is more specifically described as a glycosaminoglycan.\(^7^9,\!^8^2\) The AT binding sequence, a pentasaccharide consisting of five sugar residues of exactly defined structure within the heparin molecule, is required for interaction between the heparin molecule and the plasma protease inhibitor antithrombin.\(^7^9\)

- This AT binding sequence is present only in approximately one out of three unbound heparin molecules and accounts for essentially all of the anticoagulant activity of heparin.\(^8^8\)

- Heparin binding to antithrombin results in approximately a 1,000-fold acceleration of enzyme-inhibitor complex formation.\(^8^4\)

- In addition to thrombin inactivation, antithrombin has also been found to inactivate other hemostatic enzymes of the intrinsic coagulation cascade, including factors IXa, Xa, XIa and XIIa.\(^8^4,\!^8^9,\!^9^0,\!^9^1,\!^9^2\) Heparin accelerates each of these protease-protease inhibitor reactions.\(^8^4\)

Carmeda® BioActive Surface heparin preserves this important AT binding sequence.

- The special preparation of heparin for the End Point Attached bonding process preserves the high affinity binding site. It is present in one out of four Carmeda® BioActive Surface heparin molecules\(^9^3\) and therefore available for biological interactions with the blood.

By orienting heparin molecules and preserving active sites, End Point Attached heparin is able to participate in biological reactions with the blood, similar to heparan sulfate on the vascular endothelium.

- Heparan sulfate’s structure consists of a central protein core to which polysaccharide chains are bound.\(^7^9,\!^8^0\) Heparan sulfate chains are linked to the endothelial cells in a manner that exposes the chains so they are highly accessible to the molecules in the blood.\(^7^9\) Like heparin, a particular area of heparan sulfate, called the antithrombin binding sequence, interacts with the blood.\(^7^9\)

- Carmeda® BioActive Surface End Point Attached heparin molecules are oriented to the blood in a manner similar to that of heparan sulfate on the vascular endothelium (Figure 9). The heparin molecules protrude into the blood in a manner that allows their AT binding sequences to interact with the blood.

- A limitation of other types of heparin binding processes is that this important AT-binding sequence may become part of the bond between the heparin molecule and the device surface, preventing the AT-binding sequence from interacting with the blood.

The durable, non-leaching, covalent bonding process results in thromboresistance and biocompatibility throughout the extracorporeal circulation procedure.

- A covalent bond is created when two atoms share one or more pairs of bonding electrons.

- The covalent bonds of the End Point Attached heparin bonding process include a shared electron of the heparin biosurface and a shared electron of the device material (Figure 9).

- The Carmeda® BioActive Surface covalent bonds are strong and stable, resulting in a heparin biosurface that does not wash off during extracorporeal circulation.\(^4^6,\!^5^1,\!^8^3,\!^8^6\) This ensures that End Point Attached heparin molecules are available to provide thromboresistance and biocompatibility throughout the extracorporeal procedure.

![Figure 9 Orientation of Heparan Sulfate and End Point Attached Heparin (Carmeda® BioActive Surface): Schematics](image)

![End Point Attached Heparin Molecule](image)

Carmeda® BioActive Surface mimics additional characteristics of the vascular endothelium.

- **Negative charge.** Similar to the vascular endothelium, Carmeda® BioActive Surface is negatively charged due to the negative charge of its heparin molecules.

- **Hydrophilicity.** Heparin is a hydrophilic, or water-attracting, molecule. Heparin molecules provide Carmeda® BioActive Surface with hydrophilic characteristics, as does the biosurface’s hydrophilic priming layer.
Theory of function of Carmeda® BioActive Surface

By orienting heparin molecules and preserving active sites, End Point Attached heparin is able to interact with blood.

- One of the best known roles of heparin is binding with antithrombin (AT), a normal physiological inhibitor of the coagulation cascade (Figure 10A).
- Not only is AT a well known inhibitor of thrombin, it also inhibits other hemostatic enzymes of the intrinsic coagulation cascade, including factors IXa, Xa, Xla and XIla.84,89,90,91,92
- Antithrombin in the blood can inhibit coagulation factors without heparin, but at relatively slow rates. When AT binds to heparin at its active site, it increases its affinity for coagulation factors in the coagulation cascade by at least one thousand times84 (Figure 10B).
- Attachment of the activated coagulation factor to AT forms harmless inactive complexes, which are no longer available to participate in or trigger other events in the coagulation cascade (Figure 10C).
- Inactive AT coagulation factor complexes are then released from the immobilized heparin and swept away from the site by flowing blood (Figure 10D).
- The End Point Attached heparin molecule is not consumed in this reaction and remains on the surface, available to repeat this cycle (Figure 10E).

Like vascular endothelium, End Point Attached heparin inhibits Factor XII at the initiation, or “contact phase,” of the coagulation cascade.

- Carmeda® BioActive Surface’s high affinity heparin binds Factor XII and inhibits its conversion to activated Factor XIla47 (Figure 11).
- End Point Attached heparin mediates inhibition of the coagulation cascade prior to prothrombin activation, as suggested by research finding no clotting and no measurable amounts of thrombin-antithrombin complex (TAT) in closed test loops of End Point Attached heparin bonded tubing circulating recalcified blood plasma.56
- Experiments with endothelial lining in segments of harvested human saphenous vein demonstrated binding of FXII and inhibition of its activated form in the presence of AT.94

Inhibiting the coagulation cascade at its start may have a more profound effect on thrombus formation than inhibiting factors toward the cascade’s end by mitigating the amplifying effect of the coagulation cascade.

- FXII adsorption, activation and almost instantaneous AT binding occur on End Point Attached heparin, resulting in rapid inhibition of α-FXIIa by the AT bound to the surface. This has been found to prevent formation of kallikrein and β-FXIIa, which subsequently prevents feedback triggering of FXII and activation of adsorbed FXI.95
- Inhibiting Factor XII is a more efficient means of preventing thrombus than inhibiting thrombin after the amplifying effect has greatly increased Factor XII concentration.

Figure 10
Theory of Function: End Point Attached Heparin-Antithrombin-Coagulation Factor Binding

The End Point Attached heparin bonding method preserves the active sequence of immobilized heparin so it can interact with the blood elements, including antithrombin (AT).

When heparin binds to AT, the nature of AT changes. The resulting heparin-AT complex has a much higher affinity for coagulation factors than AT alone. The rate at which the heparin-AT complex increases its affinity for coagulation factors is 1,000 times faster than AT alone.

For example, the coagulation factor thrombin (Factor II) in the blood flowing through the circuit binds to the heparin-AT complex and becomes deactivated (Factor Ila).

The thrombin-AT complex detaches from the heparin molecule and continues to flow through the circuit. This complex is eventually metabolized by the body.

Similar to naturally occurring heparan sulfate on the vascular endothelium, the immobilized 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.
Inhibition of Factor XII not only inhibits thrombosis, it inhibits other body defense systems.

- Reduced thrombogenicity has been demonstrated with Carmeda® BioActive Surface bonded extracorporeal circulation circuits52 (Figure 12).
- In addition to activation of the intrinsic coagulation system (Figure 13), the plasma contact activation system is involved with triggering other enzymatic systems such as the fibrinolytic, complement and kallikrein/kinin systems79 (Figure 14). The angiotensin/renin systems are also affected.79
- Inhibition of Factor XII therefore not only inhibits thrombus formation, it also inhibits other body defense systems. This helps explain how Carmeda® BioActive Surface may improve the broader mechanism of overall biocompatibility, which ultimately may reduce the whole body inflammatory response.

Like systemically administrated heparin, End Point Attached heparin inactivates thrombin and Factor Xa in the presence of AT.

- End Point Attached heparin inactivates thrombin and Factor Xa in the presence of AT.56,96
- Similar to systemic heparin, End Point Attached heparin’s inhibitory capacity is not observed in the absence of AT.56

**Figure 11**

**Inhibition of Factor XIIa on High-Affinity Heparinized Surfaces**47

Mean surface adsorbed Factor XII and Factor XIIa on tubing samples bonded with 1) End Point Attached heparin, including both high and low affinity molecules or 2) End Point Attached heparin containing low affinity molecules only. Samples were incubated in *vitro* with 200 μl normal citrated human plasma. (Y-axis represents adsorbance units after 5 minutes incubation with a chromogenic substrate).

- Both heparin surfaces similarly adsorbed FXII from plasma but on the low affinity heparin surface, a major portion of surface-bound FXII was recovered in its enzymatically active form FXIIa. In contrast, only trace amounts of FXIIa were recovered from the surfaces bonded with both high and low affinity heparin.
- Surface-associated enzymatic activity was not detected when FXII-deficient plasma was used in experiments.
- Conversion of FXII to FXIIa was not prevented when standard heparin or low molecular weight heparin was added to the plasma.
- Findings suggest that high affinity heparin applied using the End Point Attached bonding method:
  - Binds Factor XII
  - Prevents Factor XII from becoming activated (FXIIa)

**Figure 12**

**Carmeda® BioActive Surface Reduces Thrombogenicity of the Extracorporeal Circuit: Ex vivo Experiment**52

- The thromboresistance of Carmeda® BioActive Surface (CBAS) applied to the entire extracorporeal circuit during 6 hours of extracorporeal support was studied in an *ex vivo* experiment with calves undergoing partial bypass (flow rate 2 l/min) receiving either a CBAS bonded circuit (n=2) or an uncoated circuit (n=2).
- Animals received only one bolus injection of heparin (250 IU/kg) before cannulation with no further heparin administered.
- Findings:
  - Uncoated group: Heparin activity disappeared at 250 minutes of bypass. Plasma fibrinopeptide A (FPA) levels started increasing after 60 min and continued to increase to 9 nM at which point the experiments were terminated at 255 minutes because the oxygenator was occluded with fibrin clots. Lung tissue biopsy indicated that most of the blood vessels in the sample were partially or completely occluded with fibrin. An accumulation of neutrophils was noted.
  - CBAS group: Heparin activity disappeared at 180 minutes. FPA levels started to increase at a runtime of 150 minutes and reached 4.5 nM at the scheduled termination of the experiment, 360 minutes. Lung tissue biopsy showed no fibrin deposition. An accumulation of neutrophils was found.
- Findings suggest that Carmeda® BioActive Surface bonding greatly reduced the thrombogenicity of the extracorporeal circulation circuit.

**Figure 13**

**Plasma Coagulation Pathways**

Carmeda® BioActive Surface's beneficial impact is associated with reduced activation of the coagulation system's intrinsic, or "contact activation," pathway. Measures to reduce activation of both the intrinsic and extrinsic pathways are considered in comprehensive strategies to reduce CPB-related morbidity.

- The intrinsic pathway is activated when blood comes into contact with a non-endothelial surface.
- Extrinsic pathway activation occurs when tissue factor is released into the circulation from damaged tissue.
- For each pathway, a series of reactions occurs that result in the activation of Factor X.
- The intrinsic and extrinsic pathways converge with the activation of Factor X and form a common pathway. Additional reactions occur that result in the formation of thrombin, which then cleaves fibrinogen to form fibrin, resulting in clot formation.
Unlike the response to systemically administered heparin, thrombin inactivation by End Point Attached heparin occurs at the device surface and not in the bulk of the blood circulating through the extracorporeal circuit.

- Thromboresistant properties of End Point Attached heparin depend, in part, on the inhibition of initially formed trace amounts of locally produced thrombin that are necessary for propagation of the blood coagulation process. 97
- While End Point Attached heparin inhibits the initial contact activation enzymes through antithrombin-mediated mechanisms, heparin in solution does not have this beneficial effect on contact activation. 98
- Contribution of End Point Attached heparin to neutralization of fluid phase thrombin has been found to be negligible. 97

Both high- and low-affinity heparin molecules play a role in End Point Attached heparin's inhibitory function.

- The density of AT on both the high and low affinity heparin molecules determines the Factor Xa inhibition capacity. 93
- The amount of AT on high affinity heparin sites limits the rate of Factor Xa inhibition. 93
- These findings suggest that during the inhibition of Factor Xa, there is continuous surface diffusion of AT from low affinity sites to high affinity sites. 93

Improved complement compatibility is associated with End Point Attached heparin.

- Blood exposure to artificial circuits results in activation of the complement system (Figure 15), mainly through the alternative pathway. 77 Complement system activation plays a role in the inflammatory response and is associated with CPB patient morbidity. 99
- End Point Attached heparin has been found to reduce complement activation in both clinical and laboratory studies. 4,5,39,58,63,64,100,101

Reduced leukocyte activation is found with End Point Attached heparin bonded surfaces.

- Leukocytes play a role in the inflammatory response and may become activated with exposure to artificial surfaces. 67,73 Leukocyte activation occurs by a number of pathways, including the complement cascade and the contact system. 103
- End Point Attached heparin has been found to reduce activation of leukocytes in clinical and laboratory investigations, including granulocytes, 4,38,42,61,63,64,111,112 eosinophils, 113 and monocytes. 103,114

End Point Attached heparin bonded surfaces are platelet-friendly, with improved platelet preservation and less platelet activation.

- Platelet activation during extracorporeal circulation is caused by platelet interaction with thrombin, contact with non-endothelial surfaces and contact with platelet-activating factor produced by a variety of cells. 71 Increased postoperative bleeding times are associated with loss of platelet numbers and function. 71
- Better platelet count preservation and reduced platelet activation have been demonstrated in clinical and laboratory investigations of End Point Attached heparin surfaces. 34,40,42,51,54,55,65,115,116 Reduced platelet adhesion has also been noted. 117,118
Figure 16
Hemocompatibility of Carmeda® BioActive Surface: Comparison of Soluble and Surface Adsorbed Markers of Hemocompatibility

Complement System
Terminal Complement Complex (soluble marker)
Significantly less terminal complement complex formation occurred with Carmeda® BioActive Surface bonding, indicating less complement activation. (p <0.05)

C3-Complement (surface adsorbed marker)
Significantly reduced complement activation occurred with End Point Attached heparin, suggested by reduced surface adsorption of complement protein C3 on the Carmeda® BioActive Surface bonded samples. (p <0.01)

Neutrophils
PMN-elastase-alpha 1-PI (soluble marker)
The Carmeda® BioActive Surface group had significantly lower PMN-elastase release, indicating less neutrophil activation. (p <0.05)

Kallikrein System
High-molecular-weight-kininogen (surface adsorbed marker)
Improved hemocompatibility, suggested by significantly greater surface adsorption of the contact factor high-molecular-weight Kininogen (HMWK), was found with Carmeda® BioActive Surface bonding. (p <0.05)

Cytokines
Interleukin 1-β (soluble marker)
Blood cell secretion of the pro-inflammatory cytokine IL-1β was significantly reduced in the Carmeda® BioActive Surface samples. (p <0.01)

Coagulation System
Prothrombin Fragment 1+2 (soluble marker)
Less coagulation activation occurred with Carmeda® BioActive Surface bonding, suggested by significantly lower prothrombin fragment F1+2 levels. (p <0.01)

Fibrinogen (surface adsorbed marker)
Significantly lower adsorption of fibrinogen on the Carmeda® BioActive Surface bonded surfaces occurred, compared to uncoated surfaces, also provided evidence of reduced thrombogenicity with End Point Attached heparin. (p <0.01)

Platelets
β-Thromboglobulin (soluble marker)
Levels of βTG were five times greater in the uncoated samples compared to the Carmeda® BioActive Surface bonded samples, suggesting less platelet activation with use of End Point Attached heparin surfaces. (p <0.01)

Fibronectin (surface adsorbed marker)
Reduced thrombogenicity on Carmeda® BioActive Surface bonded surfaces was suggested by significantly lower adsorption of the plasma protein fibronectin. (p <0.01)

Comparison of soluble markers and surface adsorbed markers of blood activation measured in samples taken from Carmeda® BioActive Surface bonded and uncoated test loops through which heparinized human whole blood was circulated for up to 120 minutes. Carmeda® BioActive Surface (CBAS) was found to favorably alter the composition of surface adsorbed proteins and was also associated with a reduction in complement, coagulation, neutrophil and platelet activation (Weber N. Biomaterials 2002; 23:429-439).
End Point Attached heparin bonding process: an overview

Heparin bonding is carefully performed to provide the unique features of Carmeda® BioActive Surface that are important to its biological role:

1.) Heparin is covalently bonded, preventing its release, or “leaching,” from the surface
2.) The End Point Attachment bonding process allows the polymeric molecules of heparin to achieve conformations necessary for their anticoagulant function so they can perform in a predictable and reliable manner.

Sophisticated End Point Attached heparin bonding process

Prime coat:
- Alternating layers of high molecular weight ionic polymers polyethyleneimine (PEI) and dextran sulfate are deposited on the device surface via electrostatic adsorption. This provides a consistent substrate that allows the Carmeda® BioActive Surface to be applied to a variety of device materials, including plastics and metals.

Carmeda® BioActive Surface
- Uncrosslinked polyethyleneimine is laid over the prime coat via electrostatic aqueous adsorption. It tenaciously attaches to the artificial surface and provides a large number of amine binding sites for covalent attachment of heparin.
- Heparin isolated from porcine mucosa is prepared for End Point Attachment by controlled and selective cleavage of the molecules, giving rise to formation of chemically reactive aldehyde groups. The aldehyde groups are located at the reducing terminus of the heparin molecules, thereby preserving the heparin molecule’s biologically active structures.
- The prepared heparin with its aldehyde end-groups is reacted with the primary amino groups on the prepared surface to form a Schiff’s base which undergoes chemical reduction, converting to a stable covalent bond.
- At this point, the heparin is covalently bound to the artificial surface on one end via the polyethyleneimine layer. The other end is in a sterically “free” state so that it is “available” to interact with the antithrombin in the circulating blood. The surface immobilization of heparin by End Point Attachment through a covalent bond allows maximum exposure of the blood elements to its anticoagulant active sequence.

Aqueous, solvent-free manufacturing methods

The Carmeda® BioActive Surface process uses aqueous solutions, mild pH and moderate temperatures. No organic solvents are involved. Coating processes are designed and controlled to ensure that coated devices are uncompromised in meeting their established performance standards.

Table 6
Heparin Stability and Activity Assessment

Medtronic uses two tests during manufacturing to verify both the stability and activity of the Carmeda® BioActive Surface heparin bonding process.

Qualitative testing
A heparin-sensitive O-toluidine blue dye is flushed through treated devices to qualitatively assess the uniformity of the heparin bonding process. When the blue dye is picked up by the heparin, it turns a distinctive purple color, indicating heparin on the surface.

Quantitative testing
A quantitative assay is performed in which human thrombin and antithrombin are used to measure the units of thrombin inhibited per square centimeter of the surface area treated. This test, performed using a spectrophotometer to measure thrombin, can be used as a direct measure of heparin activity.
Pediatric patients to adults: Carmeda® BioActive Surface’s broad clinical applications

For pediatric patients to adults, Carmeda® BioActive Surface is an important component of life-saving and life-enhancing procedures performed using extracorporeal circulation. Its non-leaching, durable End Point Attached heparin provides thromboresistance and biocompatibility during routine as well as complex procedures.

| Table 7 Medtronic Extracorporeal Circulation Technologies Available with Carmeda® BioActive Surface |
|---------------------------------|---------------------------------|
| Oxygenators                     | Resting Heart® System           |
| Centrifugal blood pumps         | Custom tubing sets              |
| Cardioplegia delivery systems   | Closed chest support system     |
| Arterial filters                | Hemodynamic support system      |
| Reservoirs                      | Cannulae                        |
| Flow probes                     | Cannulae adapters               |
| O₂ saturation cells             |                                 |
Can extracorporeal circulation be improved?  
Clinical and scientific evidence on the impact of Carmeda® BioActive Surface

Numerous clinical and scientific studies highlight the favorable impact of Carmeda® BioActive Surface on interactions between blood and artificial surfaces of extracorporeal circuits as well as its associated benefits for improved clinical outcomes (Table 8). Due to this extensive body of evidence, leading clinical teams around the world incorporate Carmeda® BioActive Surface into their comprehensive strategies for improving extracorporeal circulation procedure outcomes.

Carmeda® BioActive Surface was developed to minimize one contributor to extracorporeal circulation-related morbidity: the activation of blood when it comes in contact with artificial materials that line extracorporeal circuits. However, it does not mitigate the effects of other potential sources of extracorporeal circulation-related morbidity, such as the return of unprocessed cardiotomy suction blood directly to a pump. Differences in reported efficacy and associated clinical outcomes for heparin bonded circuits may be due to variations in cardiopulmonary bypass techniques.

Table 8
Clinical and Scientific Findings: Carmeda® BioActive Surface

Carmeda® BioActive Surface is the most extensively 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, including:

- Less blood product use
- Less perioperative blood loss
- Shorter ventilator time and reduced post-operative peak airway pressures
- Shorter ICU and hospital length of stay
- Less postoperative body temperature rise
- Fewer postoperative neurocognitive deficits
- Significantly greater urine output during CPB
- Lower costs, as related to improved clinical outcomes
- Less negative impact on the body’s defense systems, including the:
  - Contact system
  - Coagulation system
  - Fibrinolytic system
  - Complement system
  - Cytokine proteins
- Reduced impact on the blood’s formed elements, including:
  - Platelets
  - Red blood cells
  - Leukocytes

Figure 18
Carmeda® BioActive Surface’s Role During Extracorporeal Circulation

Carmeda® BioActive Surface is used in comprehensive strategies for reducing CPB-related morbidity by providing thromboresistance and biocompatibility where blood comes in contact with artificial surfaces.

Carmeda® BioActive Surface: Bibliography of published clinical and scientific studies on End Point Attached heparin technology

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<td><strong>Pediatric clinical</strong></td>
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**Bibliography of published clinical and scientific studies on End Point Attached heparin technology.**

These published clinical and scientific studies on End Point Attached heparin technology report findings from controlled in vitro and in vivo experiments as well as from clinical studies on the use of Carmeda® BioActive Surface bonded circuits during adult and pediatric extracorporeal circulation.

**Experimental in vitro**

**2007 - 2004**


**2003 - 2002**


**2001 - 2000**


**1999 - 1998**


**1997 - 1996**


1995 – 1994


1993 - 1992


1991 – 1990


1987 – 1983


Experimental in vivo

2003 – 2002


Meinhardt JP, Annich GM, Miskulin J, Kawai T, Ashton BA, Bartlett RH. Thrombogenicity is not reduced when heparin and phospholipid bonded circuits are used in a rabbit model of extracorporeal circulation. ASAIO J. 2003;49(4):395-400.


1998 – 1996


1993 – 1992


Adult—clinical

2005–2004


2003–2002


2001–1999


1998–1997


1996 – 1995


1994 – 1993


Pediatric—clinical

2004 – 2003


2000 – 1997


Reducing patient exposure to DEHP: the impact of Carmeda® BioActive Surface

Carmeda® BioActive Surface reduces patient exposure to DEHP during extracorporeal circulation, in addition to providing thromboresistance and biocompatibility.

Extracorporeal circulation procedures, including extracorporeal membrane oxygenation (ECMO) and cardiopulmonary bypass (CPB), result in large exposures of patients to DEHP. DEHP (di(2-ethylhexyl) phthalate) is a plasticizer, which is frequently added to the PVC (polyvinyl chloride) material used in medical devices to provide critical characteristics such as softness and flexibility. PVC without a plasticizer is hard and rigid.

Certain procedures pose the highest risk of patient exposure to DEHP, including ECMO in pediatrics and cardiac surgery procedures using cardiopulmonary bypass. The male fetus, male neonate and the peripubertal male have been identified as high risk for exposure to DEHP. This risk determination is based on laboratory studies that have found an association between DEHP exposure and abnormal development of the male reproductive system and production of normal sperm in young animals of certain types of rodents. Controversy exists regarding the applicability of these animal models and study findings to humans.

Limiting DEHP exposures in patient populations considered to be at risk has been recommended by the U.S. Food and Drug Administration (FDA) and by Health Canada. However, both organizations caution that procedures with a high risk for DEHP exposure should not be avoided simply due to the possibility of health risks associated with DEHP exposure, as the risk of not doing a needed procedure is far greater than the risk associated with exposure to DEHP.

Heparin biosurfaces: an option to reduce DEHP leaching from extracorporeal circulation circuits.

Clinical and laboratory studies suggest that the use of heparin coatings, particularly covalently bonded heparin coatings, significantly reduces leaching of DEHP from PVC components used for extracorporeal circulation procedures.

- Karle, et. al. (1997). Almost no DEHP leaching was detected in blood samples taken from infants undergoing ECMO therapy using circuits made with tubing coated with Carmeda® BioActive Surface. In contrast, DEHP was extracted from blood samples taken from infants undergoing ECMO using uncoated circuits.

- Haishima Y, et. al. (2004). DEHP release into circulating bovine blood was significantly suppressed in test circuits made with PVC tubing coated with covalently bonded heparin. A considerable amount of DEHP was released from test circuits made using two different manufacturers’ uncoated PVC tubing and also from a test circuit made using PVC tubing coated with an ionically bonded heparin.

While research finds that heparin biocompatible surfaces reduce leaching from DEHP, it also suggests there may be differences between types of heparin biocompatible surfaces. In testing conducted by scientists and engineers in the laboratories of the Medtronic Energy and Component Center and Medtronic Perfusion Systems (Minneapolis, Minnesota, USA), the impact of Medtronic’s heparin biosurfaces Carmeda® BioActive Surface and Trillium® Biosurface on DEHP leaching from PVC tubing commonly used in extracorporeal circulation circuits was measured and compared.
Determination of reduction in DEHP leaching from PVC tubing attributed to Carmeda® and Trillium® Heparin Biocompatible Surfaces.

Objective: To quantitatively determine the reduction in leaching of di(2-ethylhexyl) phthalate (DEHP) plasticizer from PVC tubing attributed to the use of Carmeda® BioActive Surface or Trillium® Biosurface.

Test materials/methods: Test circuits were constructed that each contained a sample of one of four types of tubing (length: 20 feet, inner diameter 3/8 inch, wall thickness 3/32 inch): uncoated PVC, Carmeda® BioActive Surface coated PVC, Trillium® Biosurface coated PVC or silicone. Each test circuit also included additional silicone tubing for placement in the peristaltic roller pump raceway, a silicone shunt (used to re-circulate blood in the non-PVC parts of the circuit until a temperature of 37°C was reached), polycarbonate connectors, a heat exchanger and a 1-liter glass reservoir with an HDPE (high density polyethylene) tubing insert (Figure 19).

Six circuits were tested for each tubing type. For each test circuit, 1 liter of undiluted blood from an individual donor animal was circulated using a peristaltic roller pump for 24 hr (4 L/min, 37°C). Blood from each donor animal was used for a test of each circuit.

Blood samples were collected from each circuit at 2 hr, 6 hr and 24 hr of circulation time. The blood samples were extracted and analyzed for DEHP content using high performance liquid chromatography (HPLC) with mass spectral detection.

Results: DEHP concentrations, measured in parts per million (ppm), increased over time in all PVC test circuits but were lower in the test circuits coated with heparin biosurfaces (Figure 20; Table 9). DEHP leaching was reduced by 95% or more in Carmeda® BioActive Surface coated tubing compared to uncoated PVC Tubing, with significantly less leaching found in samples studied at all time points (Table 10). A reduction in DEHP leaching of 1%-12% was measured in the Trillium® Biosurface circuit samples (Table 10), with significant differences from uncoated PVC tubing noted only at 24 hr (Table 9). The highest DEHP levels were detected in the uncoated PVC tubing circuit samples. As expected, no DEHP was detected in the samples from silicone circuits.

Conclusion: Carmeda® BioActive Surface is a significant barrier to DEHP leaching from flexible PVC. DEHP reduction due to the Trillium® Biosurface was not substantially or significantly different than that found with uncoated tubing. It cannot automatically be assumed that all heparin coatings have the same impact on DEHP leach reduction. Each coating, including heparin coatings and other types of coatings, must be evaluated separately to determine its abilities as a barrier to DEHP.

Table 9
Summary of DEHP Leaching Data from Three Types of PVC Tubing
mean ± standard deviation (ppm)

<table>
<thead>
<tr>
<th>Interval (hr)</th>
<th>Uncoated</th>
<th>Carmeda®</th>
<th>Trillium®</th>
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<tr>
<td>2</td>
<td>5.87 ± 0.62</td>
<td>0.20 ± 0.05*</td>
<td>5.84 ± 0.63</td>
</tr>
<tr>
<td>6</td>
<td>19.93 ± 2.20</td>
<td>0.42 ± 0.07*</td>
<td>18.20 ± 1.44</td>
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<tr>
<td>24</td>
<td>70.57 ± 9.57</td>
<td>1.64 ± 0.23*</td>
<td>62.41 ± 8.10*</td>
</tr>
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* Statistically significant difference compared to uncoated PVC tubing (p < 0.05)
Common clinical topics

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**Patient size and weight restrictions**

There are no size or weight restrictions for use of Carmeda® BioActive Surface. Pediatric patients to adults may receive the benefits of extracorporeal circulation procedures using technologies covalently bonded with non-leaching Carmeda® BioActive Surface Endpoint Attached heparin.

In contrast, labeling for devices coated with ionically bonded heparin have included patient size restrictions. Ionically bonded heparin leaches over time, contributing to heparin in systemic circulation.

**Duration of use**

In the United States, Medtronic Perfusion Systems’ extracorporeal circulation technologies, with the exception of silicone membrane oxygenators, are indicated for up to six hours of use. Extracorporeal circulation technologies bonded with Carmeda® BioActive Surface are accordingly indicated for use up to six hours.

In countries outside the United States, consult your Medtronic Representative and product labeling for more specific information about the duration of use for a particular product in your area.

**Reprocessing/resterilization**

Devices bonded with Carmeda® BioActive Surface are intended for single use only and should not be reprocessed or resterilized. The integrity and performance of Carmeda® BioActive Surface, as well as the coated device, may become compromised if subjected to reprocessing.

**Shelf life**

Medtronic Perfusion Systems technologies, including Carmeda® BioActive Surface bonded technologies, should never be used beyond their labeled expiration date. This date is established after carefully evaluating device design, material characteristics and performance requirements and after rigorous tests have been performed to establish that the technology meets requirements for safe and effective use within its stated shelf life parameters. Shelf life may differ from device to device.

Devices that have reached their labeled expiration date should be discarded. They should never be used, reprocessed or resterilized.

**Bonded circuit component selection**

In order to maximize the benefits of improved biocompatibility, all blood contact surfaces should be exclusively heparin bonded with Carmeda® BioActive Surface.

A Medtronic Representative may be consulted for information on Carmeda® BioActive Surface bonded extracorporeal circuit component availability.

**Compatibility with other types of coated circuit components**

Medtronic offers two non-leaching heparin biocompatible surfaces for our extracorporeal technologies: Carmeda® BioActive Surface and Trillium® Biosurface. Based on Medtronic’s knowledge of the characteristics and performance of these two biocompatible surfaces, components coated with Carmeda® BioActive Surface and Trillium® Biosurface may be combined within the same extracorporeal circuit.

Because Medtronic does not have control over the quality, safety or performance of other manufacturer’s devices, we cannot comment on the use of Medtronic’s heparin bonded technologies with other manufacturers’ devices.

**Oxygenator gas transfer**

All oxygenators manufactured by Medtronic must meet performance requirements for safe and effective clinical use, including oxygenators with coated fiber bundles. As demonstrated during hundreds of thousands of hours of successful patient use, Carmeda® BioActive Surface does not have a clinically significant impact on gas transfer performance requirements for safe and effective cardiopulmonary bypass.

Information on any Medtronic oxygenator’s gas transfer performance characteristics may be found in the device’s product labeling.

**Antifibrinolytics**

Reports describing use of antifibrinolytic agents such as aprotinin,115,131,132 or aminocaproic acid,40,48,133 in clinical and experimental studies with Carmeda® BioActive Surface bonded devices have been published in the literature.

Medtronic, as a medical device manufacturer, does not make specific recommendations regarding the use of antifibrinolytic agents with Carmeda® BioActive Surface bonded extracorporeal technologies. This decision is to be made by a physician, based on clinical judgment of the requirements for a particular patient in a particular clinical situation.
Anticoagulation protocols

Medtronic, as a manufacturer of Carmeda® BioActive Surface bonded extracorporeal technologies, does not recommend or promote specific heparin regimens for use with any of our technologies. The amount of heparin used during extracorporeal circulation is strictly a physician decision based upon the benefits and risks for a specific patient and procedure.

A strict anticoagulation protocol should be followed, and anticoagulation routinely monitored, during all extracorporeal procedures using Carmeda® BioActive Surface bonded technologies. The benefits of extracorporeal support must be weighed against the risks of systemic anticoagulation and must be assessed by the prescribing physician. Adequate heparinization must be maintained before and during the extracorporeal procedure. Use of a heparin management system may be considered for determining precise, patient-specific heparin and protamine requirements.

Protamine interactions

Protamine inactivates heparin, including the heparin in Carmeda® BioActive Surface. Immobilized heparin that has been reversed by protamine is not fully able to interact with the blood and may not provide its full benefits for thromboresistance and biocompatibility.

Heparin-induced thrombocytopenia (HIT) patients

The use of Carmeda® BioActive Surface technologies for patients with heparin-induced thrombocytopenia (HIT) is a physician decision based on the patient’s specific clinical condition and the clinical team’s comprehensive patient management strategy.

Institutions rarely encounter patients with HIT who require cardiac surgery on an emergent basis. Accordingly, large, controlled investigations of the use of Carmeda® BioActive Surface during extracorporeal circulation procedures for HIT patients have not been published to date. Published case reports have described the use of Carmeda® BioActive Surface bonded devices with alternative anticoagulation protocols for patients with HIT. However, findings from individual case studies cannot be generalized to all patients.

Heparin source

Carmeda® BioActive Surface is manufactured using porcine heparin. Porcine heparin has always been used for the manufacture of Carmeda® BioActive Surface.
References


Instructions for Use: Bentley® Spiral Gold Hollow Fiber Oxygenator with Duraflo® II Treatment. PN007715-01 A. Baxter Healthcare Corporation, Bentley Division. Irvine, California, 05/30/95.


