CLINICAL IMPLICATIONS OF BASIC RESEARCH

Elizabeth G. Phimister, Ph.D., *Editor*

Sticking with Synthetic Tissue Sealants

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Tissue reanastomosis and wound closure are vital steps in surgery. Similarly, in percutaneous intervention, localized hemostasis is essential. Traditionally, sutures and staples have been used for tissue approximation and closure. Despite their basic efficacy, these tools have limitations that include the added trauma to tissue during placement and the difficulty of deployment in small spaces and tight geometries.

Lang et al.[1] describe a new tool for tissue sealing and repair: a fluid, blood-resistant tissue glue for use in surgical and minimally invasive cardiovascular therapeutic procedures. This "glue" is a hydrophobic light-activated adhesive (HLAA) that consists of a biocompatible, biodegradable hydrophobic prepolymer, poly(glycerol sebacate acrylate), which when mixed with a photoinitiator and exposed to ultraviolet light may be cross-linked in situ. What is new and advantageous about HLAA is that it can be applied as a liquid before a procedure is performed and then activated on demand to adhere, cure, and bond. The material itself has innate physiochemical properties of hydrophobicity and viscosity, both before and after curing, so that it remains in the form of a bulk continuum that will neither solvate nor dissolve, despite being in an aqueous or intravascular blood environment, even when subjected to pressure and flow. The resultant adhesive is soft and elastic, with material properties akin to underlying tissues, yet with significant adhesive and cohesive strength, providing an increased power of adhesion that is nearly three times as great as that of current commercially available fibrin sealants.

Lang et al. engineered these mechanical and adhesive properties by conducting a series of optimization experiments. The viscosity of HLAA in its fluid state was tested at several shear rates, and a minimal change of viscosity was observed; slight shear-thinning properties were exhibited that are well suited to the achievement of good fluidity, a quality that is favorable for deployment in the cardiovascular system. Ultraviolet cross-linked HLAA polymeric films underwent compression testing so that the effect on Young's modulus (a measure of flexibility) could be examined, and an initial slight increase was revealed, although overall modulus remained constant with additional compression. "Pull-off" adhesion testing revealed good adhesion strength, which was achieved by establishing an optimal mixing ratio of acrylate groups per glycerol molecule, combined with 5 seconds of exposure to ultraviolet light at an intensity of 0.38 W per square centimeter. Stronger bonding required curing for up to 30 seconds. The range of these cure durations is clinically reasonable for ensuring adhesion once the agent is positioned correctly, although it is clear that rapid curing is a favorable and essential feature given the fluidity of the HLAA precure. In vitro and in vivo biocompatibility testing revealed a response profile similar to that of fibrin glue.

The investigators compared the thrombogenic potential of HLAA and the biodegradable elastomer poly(glycerol sebacate urethane) (PGSU) when used as patch matrixes with the thrombogenic potential of glass, a highly thrombogenic reference material. They concluded that both HLAA and PGSU are minimally thrombogenic; as compared with glass, they exhibit 46% and 65% less platelet adhesion, respectively. This assay provides a basic assessment of hemocompatibility; more stringent hemocompatibility testing is warranted.

Lang et al. found that HLAA bonds to cardiac and vascular tissue, clinically available patch materials (e.g., the pericardium), and polyethylene terephthalate. HLAA was found to be biocompatible with rat epicardium for a 14-day period, with no alteration of underlying cardiac function. Effective closure of a transmural defect in the left ventricular wall was noted in the

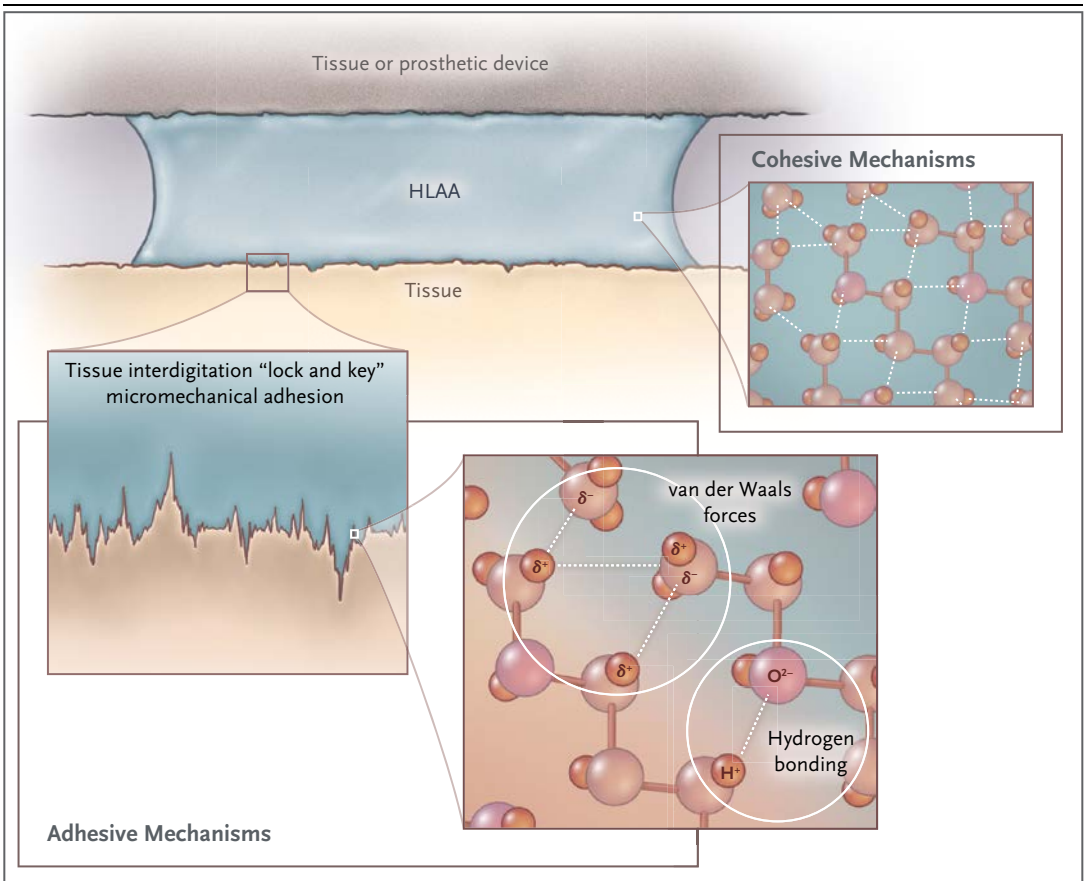

Figure 1. Mechanisms Underlying HLAA Efficiency.

The hydrophobic light-activated adhesive (HLAA) recently described by Lang et al.[1] has properties of adhesion, the attraction between dissimilar materials (e.g., between different types of body tissue or between tissue and prosthetic device), and cohesion, the attraction between the components of a material continuum. For each property, physical forces (e.g., micromechanical adhesion), chemical forces (e.g., van der Waals forces and hydrogen bonding), or both contribute to adhesive intactness and strength.

rat even though HLAA was applied to a beating heart, with accompanying exposure to blood and systemic pressure. Successful in situ attachment of an HLAA-coated patch to the intraventricular septum of the beating heart was also accomplished. Patches maintained septal adherence despite being subjected to supraphysiologic blood pressures and heart rates.

Although tissue glues and sealants have existed for more than 60 years, in the past two decades there has been dramatic growth in the development of alternatives to sutures and tissue-fastening systems and of the materials used as means of extending local wound-healing capabilities. Broadly speaking, sealants that are currently in clinical or laboratory use may be applied externally or internally, may consist of natural materials (e.g., fibrin), modified natural materials (e.g., mussel protein), or synthetic materials, may function as simple preformed glues that can be activated on demand (so that the fluid glue can rapidly cure at the target site) or as desiccated materials capable of reconstitution and swelling, may serve as hemostatic or adhesion barriers or combinations thereof, and may act as dual systems capable of both adhesion and drug delivery.[2] In the mid-1990s, a flowable, photoactivated, in situ curing hemostatic sealant similar to HLAA that was based on polyethylene glycol lactide was approved by the Food and Drug Administration, but this agent is hydrophilic and requires preparation and "surface roughening" of the underlying tissue for robust adhesion to occur.[3,4]

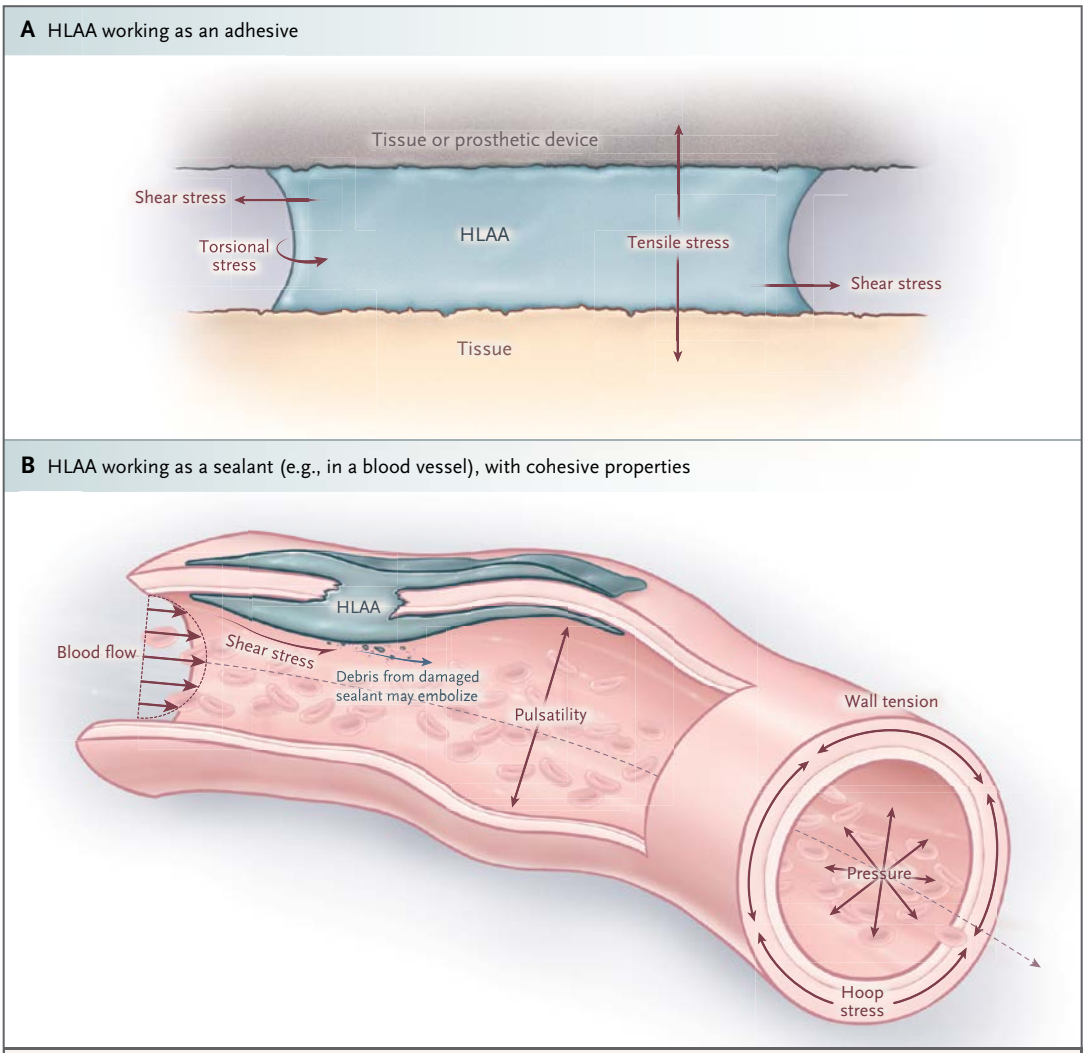

Figure 2. Stresses and Forces on a Cardiovascular Bioadhesive Agent.

Lang et al.[1] have described a new "surgical glue," HLAA, and proposed its use as an adhesive agent (Panel A) and as a sealant, with cohesive properties (Panel B). Ideally, a bioadhesive agent should have both adhesive and cohesive properties to withstand the dynamic stresses to which it is exposed. As a sealant, it is subject to stresses induced by blood flow (e.g., shear stresses that may embolize the sealant if it is insufficiently cohesive) as well as tension stresses that develop within the arterial wall and may cause the bioadhesive agent to detach and peel off (e.g., hoop stresses resulting from luminal pressure and flow pulsatility that interact with the distensible arterial wall and torsional and tensile stresses that arise from the contractions of a beating heart).

HLAA is an advanced sealant that offers many desirable properties. Its flowable nature allows it to interdigitate into tissue interstices, increasing the surface area for bonding and acting as both a physical and chemical "lock-and-key" system (Fig. 1). Interdigitation may be achieved without surface preparation or priming. The HLAA layer acts as an effective seal and barrier, preventing ingress of fluid, blood, and inflammatory cells into the bonded zone. It also appears to be nonthrombogenic — a vital feature when placed intravascularly (Fig. 2). Finally, the robust and elastomeric cohesive properties of HLAA provide a degree of compliance matching (i.e., its compliant features are similar to those of the host tissue or vessel) that is particularly valuable

in the pulsatile environment of intravascular applications.

Given the rapid advances in minimally invasive and percutaneous cardiovascular technologies (e.g., the use of stent valves and stent grafts and the use of clips, patches, occluders, endoluminal paving [the coating of the luminal surface of the vessel], and ventricular-assist devices), there is a growing need for the development of an effective hemocompatible, hemostatic adhesive that facilitates the effective deployment of these technologies. Studies such as the one reported by Lang et al. represent advances toward meeting this need.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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