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Nerve and Conduction Tissue Injury Caused by Contact with BioGlue

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Background. **BioGlue—a surgical adhesive composed of bovine albumin and glutaraldehyde—is commonly used in cardiovascular operations. The objectives of this study were to determine whether BioGlue injures nerves and cardiac conduction tissues, and whether a water-soluble gel barrier protects against such injury.**

Materials and methods. **In 18 pigs, diaphragmatic excursion during direct phrenic nerve stimulation was measured at baseline and at 3 and 30 min after nerve exposure to albumin (n = 3), glutaraldehyde (n = 3), BioGlue (n = 6), or water-soluble gel followed by BioGlue (n = 6). Additionally, BioGlue was applied to the cavoatrial junction overlying the sinoatrial node (SAN), either alone (n = 12) or after application of gel (n = 6).**

Results. **Mean diaphragmatic excursions in the BioGlue and glutaraldehyde groups were lower at 3 min and 30 min than in the albumin group ($P < 0.05$). Mean excursions in the gel group were similar to those of the albumin group ($P = 0.9$). Five BioGlue pigs (83%) and one gel pig (17%) had diaphragmatic paralysis by 30 min ($P < 0.05$ and $P = 0.3$ *versus* albumin, respectively). Coagulation necrosis extended into the myocardium at the cavoatrial junction in all 12 BioGlue pigs but only two gel pigs (33%, $P < 0.01$). Two BioGlue pigs (17%), but no gel pigs, had focal SAN degeneration and persistent bradycardia ($P < 0.01$).**

Conclusions. **BioGlue causes acute nerve injury and myocardial necrosis that can lead to SAN damage. A water-soluble gel barrier is protective.**

Key Words: **BioGlue; surgical adhesive; nerve injury; aortic dissection; glutaraldehyde; sinoatrial node.**

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INTRODUCTION

BioGlue (CryoLife, Inc., Kennesaw, GA)—a surgical adhesive composed of 10% glutaraldehyde and 45% purified bovine serum albumin—is increasingly being used in cardiovascular operations [1–5]. Compared with its predecessor, gelatin-resorcinol-formaldehyde-glutaraldehyde glue (GRFG, or "French glue"), BioGlue offers the potential advantages of easier application, stronger bonding, and less toxicity. Its reduced toxicity is attributed to the elimination of formaldehyde. Now widely available throughout the world, BioGlue was approved by the FDA in December 2001 for use in the United States as an adjunct to standard methods of achieving hemostasis in adult patients undergoing open surgical repair of large vessels, such as the aorta and the femoral and carotid arteries.

The aldehyde component of BioGlue raises concerns about BioGlue's possible toxicities. Although BioGlue is dispensed by a controlled delivery system and the components are premixed within the applicator tip where cross-linking begins, enough "free" glutaraldehyde may be dispensed to cause tissue injury upon contact. This concern is supported by a recent study by Furst et al., who evaluated concentrations of glutaraldehyde in the supernatant of polymerized BioGlue incubated in saline [6]. Reports have been published suggesting that a 25% glutaraldehyde solution can cause contact injury with the phrenic nerve, resulting in diaphragmatic paralysis, postoperative respiratory failure, and death [7]. Aldehyde-based adhesives have also been considered culprits in the development of complete heart block in patients undergoing repair of acute aortic dissections [8]. Although early animal studies with short-term follow-up [9–11] found minimal damage in tissues exposed to BioGlue, recent re-

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ports [6, 12, 13] suggest that it causes local toxicity and extensive scarring, supporting the need for further study of BioGlue's toxicities, and for a search for protective strategies. The proximity of the sinoatrial node (SAN) and the vagus, hypoglossal, superior laryngeal, and recurrent laryngeal nerves to common cardiovascular suture lines makes them vulnerable to injury if aldehyde-based adhesives are used [14]. The objectives of this study were to determine (1) whether BioGlue injures nerves and cardiac conduction tissues, and (2) whether a water-soluble gel barrier protects against such injury.

MATERIALS AND METHODS

The study protocols were approved by the Institutional Animal Care and Use Committees at both Baylor College of Medicine and the Texas Heart Institute at St. Luke's Episcopal Hospital. All animals were fully examined by a staff veterinarian before surgery and received humane care and handling in compliance with the Principles of Laboratory Animal Care formulated by the National Society for Medical Research and the Guide for Care and Use of Laboratory Animals (NIH Publication no. 85-23, revised 1996).

Anesthetic Care

Eighteen female Yorkshire pigs (age, 10 to 15 wk; weight, 31.6 ± 4.3 kg) underwent general anesthesia. The pigs were premedicated with intramuscular atropine sulfate (0.5 mg/kg), acepromazine (0.1 mg/kg), and ketamine hydrochloride (20 mg/kg). Isoflurane (2 to 6%) was administered by mask inhalation for induction. The pigs were intubated with a cuffed endotracheal tube (size, 7.0 to 8.0) and connected to a volume ventilator with a tidal volume of 10 cc/kg, a respiratory rate of 12 to 20 breaths per min, and 100% oxygen. Monitoring devices included a pulse oximeter, electrocardiography leads, and a rectal temperature probe.

General anesthesia was maintained with inhaled isoflurane (0.5 to 3.0%). To avoid interference with diaphragmatic contraction, no paralytic agents were administered. Buprenorphine (0.01 mg/kg) was given intramuscularly as needed. An 18-gauge angiocatheter was inserted into the exposed right carotid artery for blood sampling and blood pressure monitoring. Baseline electrocardiograms (ECGs), arterial blood gases, and serum potassium and magnesium levels were obtained. Abnormal laboratory values were corrected accordingly.

Phrenic Nerve Study Operative Protocol

Through a standard median sternotomy, approximately 8 cm of the right phrenic nerve was exposed along the parietal pleura near the posterior vena cava (Fig. 1). A large metallic surgical clip was attached to the superior-most aspect of the right hemidiaphragm to serve as a radiopaque marker. A radiopaque ruler (LeMaitre Stent Guide; Vascutech, Burlington, MA) was secured longitudinally on the chest and abdominal wall. Nerve stimulator electrodes (DigiStim III; Neuro Technology, Inc., Kerrville, TX) were attached directly to the proximal portion of the exposed phrenic nerve. During assessment of phrenic nerve function, the endotracheal tube was briefly disconnected from the ventilator, allowing the diaphragm to settle in a neutral position. Ventilation was resumed intermittently to keep oxygen saturation above 95%. A stimulation-response relationship between the right phrenic nerve and the diaphragm was measured by applying continuous square-wave pulsations (3 mA) for 2 s at 50 Hz. Movement of the right hemidiaphragm was recorded using video cinefluoroscopy (OEC, Salt Lake City, UT) [15]. Diaphragmatic excursion was quantified as the vertical distance the surgical clip moved during phrenic nerve stimulation (Fig. 2). All final diaphragmatic excursion values represent the mean of three separate measurements performed at 1 min intervals.

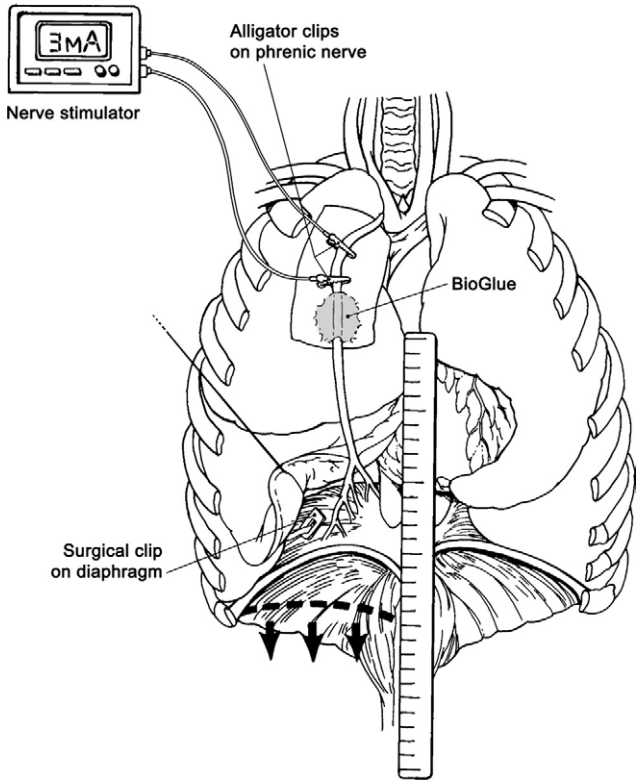

FIG. 1. Diagram illustrating the experimental model, including the exposed segment of the right phrenic nerve; the position of the nerve stimulator electrodes, diaphragmatic surgical clip, and radiopaque ruler; and the application of the BioGlue to the phrenic nerve. Diaphragmatic excursion during nerve stimulation is indicated by the broken line and downward arrows.

After baseline diaphragmatic excursions were recorded, the exposed phrenic nerve distal to the electrodes was treated with 2 mL of 10% glutaraldehyde (positive control, $n = 3$), 45% bovine albumin (negative control, $n = 3$), or BioGlue ($n = 6$). In the other six pigs, a 2- to 4-mm coating of a water-soluble gel (Surgilube; E. Fougera and Co., Melville, NY) was applied to the nerve, followed by BioGlue. BioGlue was applied according to manufacturer instructions; the investigators (SAL and JSC) were trained in the application of BioGlue by CryoLife, Inc., and have extensive experience in its clinical use during cardiovascular operations [3]. The BioGlue application device, including the preloaded cartridges, application gun, and mixing tips, was identical to that currently used in clinical practice. The individual bovine albumin and glutaraldehyde solutions for the control pigs were extracted from the preloaded cartridges. The gel was applied using a 10 cc syringe. Because of BioGlue's low viscosity, runoff was unavoidable; this runoff was continuously removed with suction during BioGlue application to avoid exposing adjacent tissues to the adhesive. Diaphragmatic excursion was remeasured 3 and 30 min after application of the glutaraldehyde, albumin, BioGlue, or gel and BioGlue.

Sinoatrial Node Study Operative Protocol

In 12 pigs, 8 mL of BioGlue was applied to a 4 cm^2 area at the cavoatrial junction overlying the SAN. In the six other pigs, the same