Myocardial Response to the Application of Tissue Adhesives. Comparison of Methyl-2-cyanoacrylate and Butyl-cyanoacrylate

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The use of plastic tissue adhesives to provide hemostasis, to seal raw surfaces, to simplify the anastomosis of various tubular structures and to reinforce insecure suture lines has been the object of intense investigation. These studies have led to wide differences of opinion among investigators as to the advisability of clinical use of adhesives. Because an occasional situation develops in which there is need for such substances in cardiovascular surgery, it was believed that additional investigation of the myocardial response to the application of these agents was warranted. These experiments compare the effect of methyl-2-cyanoacrylate with butyl-cyanoacrylate applied to the atrial and ventricular myocardium of dogs.

Materials and Methods

Experiments were performed upon 12 adult mongrel dogs that were free from serious disease. Intravenous nembutal anesthesia was administered and controlled ventilation was provided by a respirator. Electrocardiograms were taken prior to the surgical procedure, immediately following closure of the chest, and prior to sacrificing the animal.

The right pleural space was entered through a standard incision and the superior and inferior venae cavae were cirsmscribed with umbilical tapes to provide inflow occlusion when needed. The pericardium was opened widely to expose the right side of the heart. The right atrial appendage was then amputated and the cut edges were approximated with continuous silk suture. Methyl-2-cyanoacrylate was sparingly applied over the suture line by carefully squeezing it out of the small tube provided by the manufacturer. The midportion of the right atrium was then selected for application of butyl-cyanoacrylate. (This monomer was synthesized by the U. S. Army Medical Biochemical Research Laboratory** and was sterile and 98% pure.) A portion of the right atrial wall was drawn through a double angled vascular clamp and a 2-cm. atriotomy was made. By retracting the cut edges apart, the endocardium was exposed and butyl-cyanoacrylate was extruded through an 18-gauge needle into the depths of the atriotomy. Care was taken to provide a film of adhesive over the entire exposed endocardium at the same time excess was avoided. After polymerization occurred, a loose suture line of continuous silk was used to approximate the atriotomy edges.

Using inflow occlusion to prevent blood loss and to provide a dry operative field,

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a 2-cm. transverse right ventriculotomy was made and butyl-cyanoacrylate was applied to both of the cut surfaces of the ventricle. This procedure was performed quickly and precise application of the adhesive was not always possible. An attempt was made, however, to cover the entire cut surface with the smallest volume that would provide a thin layer.

Only a single figure-of-eight suture was used to approximate the ventriculotomy.

Following chest closure, air was aspirated from the pleural space. Postoperative tube drainage was not provided, nor were prophylactic antibiotic agents administered. Two of the 12 animals died; one on the second postoperative day and the other on the third. Autopsy did not reveal the cause of death in either instance. Except for these two deaths, the animals were sacrificed at intervals following the procedure and the hearts were examined. Gross photographs were taken and tissue was secured for histologic examination. Gross and microscopic findings in the heart at the end of 1, 2, 3, 9 and 20 weeks will be discussed.

1 Week. Gross: A small quantity of serosanguineous fluid was present in the pleural space. In the areas of adhesive application there were filmy adhesions between pericardium and epicardium which were easily lysed by blunt dissection. The epicardium was hyperemic except where the incisions had been made, and here was a fine lusterless, shaggy, fibrinous membrane. Within the atrium extensive thrombus was present at both sites of adhesive application (Fig. 1). The most extensive thrombus was located where the butyl-cyanoacrylate had been applied upon the endocardium. Here the thrombus was 1.5—2 cm. in thickness.
and was tenaciously attached with a broad base. Traction applied to either side of the atriotomy revealed a firm bonding at the suture line.

The epicardium of the ventricle was similar to the atrium. Extending several centimeters beyond the center of the ventriculotomy the endocardium was hyperemic (Fig. 2), but there was little visible thrombus. The cut surface through areas of monomer application showed hard granular clumps of this material firmly adherent to the myocardium.

Microscopic: Deposits of polymer were present within the atrial wall. Adjacent to this material, myocardial fibers had undergone extensive necrosis and the area was massively infiltrated with polymorphonuclear leukocytes and red blood cells (Fig. 3). A thick recent thrombus projected from the endocardial surface. The extent of the inflammation was the same whether the adhesive was applied outside or inside the atrium. A study of various tissue sections failed to demonstrate quantitative or qualitative differences in the inflammatory response elicited by the two types of adhesives.

2 Weeks. Gross: The epicardium was less hyperemic than after 1 week. Now the thrombus at the site of adhesive application was smoothed down to a broad base with conical projections and narrow tips extending into the atrium (Fig. 4). This may have been the result of fibrinolysis or the abrasive action of turbulent blood flow.

Very little thrombus was seen within the ventricle. Gross acute inflammation was manifested by patchy areas of hyperemia extending for several millimeters beyond the margins of the ventriculotomy.

Microscopic: Immediately adjacent to the adhesive, a prominent infiltration of neutrophils was still present. An occasional multinucleated giant cell and many mononuclear cells were also seen. Myocardial necrosis was less prominent than at the 1-week period. Beyond the zone of acute inflammation, fibroblasts and early fibrous tissue were seen. Microscopic changes were similar around both the methyl-2-cyanoacrylate and the butyl-cyanoacrylate.

3 Weeks. Gross: The atrium was completely free of thrombus. Extending for 4–5 mm. beyond the suture lines there was a zone of scarring which contrasted sharply

Fig. 3. After 1 week: Acute inflammatory reaction; intense infiltration of polymorphonuclear leukocytes adjacent to the tissue adhesive. (H & E ×124.)
with the normal atrium. The suture line was rigid to palpation due to the presence of residual polymer.

The ventricle had similar gross features: absence of thrombus, a zone of scarring, and residual polymer embedded within the myocardium.

Microscopic: Surrounding deposits of polymer within the myocardium was an inflammatory infiltrate consisting of large

![Image of atrial thrombus](image1)

**Fig. 4. After 2 weeks:** Atrial thrombus still present; undergoing dissolution.

![Image of cellular exudate](image2)

**Fig. 5. After 3 weeks:** Cellular exudate around deposit of polymer consists of many lymphocytes, mononuclear cells and a few polymorphonuclear leukocytes. Scar tissue is present. (H & E ×124.)
mononuclear cells, lymphocytes, and multinucleated giant cells. Myocardial fibers within and immediately adjacent to the inflammatory infiltrate were eosinophilic and contained few nuclei. Within this area and extending into the pericardium, there were fibroblasts and early fibrous tissue was forming a dense scar (Fig. 5).

9 Weeks. Gross: There was no gross evidence of acute inflammation. Adhesions between pericardium and epicardium were dense and tough. The endocardium of both the atrium and ventricle showed a prominent zone of scarring that had been seen at the 3-week period (Fig. 6, 7).

Microscopic: Devitalized myocardial fibers had been largely replaced by connective tissue, dense in some areas and in others the matrix for numerous small new blood vessels (Fig. 8). In the more vascular areas, large mononuclear cells, lymphocytes, and a few eosinophils were scattered. Microscopically there was no distinction between the reaction caused by the two adhesives.

20 Weeks. Gross: The gross findings were identical to those at 9 weeks. Residual polymer gave the scarred areas a firm feeling and was still present on the cut surface.

Microscopic: Surrounding deposits of polymer was dense fibrous tissue which had replaced myocardial fibers (Fig. 9). No inflammatory reaction was present. Interestingly, within one area of dense scar there was a focus of cartilagenous metaplasia.
Discussion

Opinions about the clinical usefulness of tissue adhesives vary from enthusiasm\(^2, ^3\) to a warning that clinical application is premature.\(^5\) Our findings confirm that the adhesive evokes a violent acute inflammatory response due to local histotoxicity.\(^6\) In the early phase, which lasts about 2 weeks, myocardial fibers adjacent to the monomer underwent coagulation necrosis and there was considerable infiltration of neutrophils. During the next several weeks the acute response resolved and polymorphonuclear leukocytes were replaced by mononuclear cells and a few scattered multinucleated giant cells. At the 3-week interval young fibrous tissue began to replace destroyed myocardial fibers. Between

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**Fig. 8.** After 9 weeks: Numerous capillaries in scar tissue around deposit of polymer. (H & E ×124.)

**Fig. 9.** After 20 weeks: Dense scar surrounds the tissue adhesive. The inflammatory reaction has cleared except for a few mononuclear cells adjacent to the adhesive.
3 and 20 weeks there was a progressive clearing of inflammatory cells and a steady maturation of the fibrous tissue until a dense tough scar resulted. In one instance this had progressed to beginning calcification.

Thrombus formation within the atrium was one of the most impressive gross findings at 1 week. The contrast between the amount of thrombus in the atrium compared to the ventricle is probably due to differences in the nature of blood flow in the two chambers. This thrombogenic property of tissue adhesives seems to preclude clinical usefulness on low pressure vessels or the atria.

It has been suggested that toxicity of the cyanoacrylate adhesives is due to the cyano radical and to the local heat generated when polymerization occurs. Supporting this thesis were the findings that by substituting a hexyl or decyl for the methyl group there was less microscopic evidence of toxicity. The higher molecular weight esters generated less heat during polymerization and evoked a transient mononuclear and giant cell response instead of the inflammatory reaction caused by methyl-2-cyanoacrylate.

The method of applying adhesive was similar to that which might be used clinically and the amount of material used was probably greater than that used by other investigators. The amount may have varied in different experiments and influenced the degree of inflammation. With our techinic both monomers caused toxic changes not distinguishable from one another. Studies using precise microtechnics should be done to compare available monomers.

The ultimate scar formation was found more extensive than expected with standard suture technics. Although no tendency toward aneurysm formation was found, Weissberg and Goetz demonstrated fusiform dilatation in large muscular arteries when methyl-2-cyanoacrylate had been applied to an area from which the adventitia had been removed.

Despite the irritating and histotoxic effects of monomers on the myocardium, there were no significant changes in electrocardiograms during the postoperative period.

It is difficult to apply tissue adhesives to a bleeding, irregular surface, such as would be the requirement in cardiovascular surgery.

Summary

Methyl-2-cyanoacrylate and butyl-cyanoacrylate are histotoxic and thrombogenic. Over a period of weeks there is a progressive resolution of the inflammation evoked and an organization of the thrombus. An extensive dense scar is formed at the site of application.

The unfavorable tissue response precludes clinical application of these tissue adhesives except in desperate situations when suture technics are inadequate.

References