

# Rabbit Model for Capsular Contracture: Development and Clinical Implications

[EXPERIMENTAL: ORIGINAL ARTICLES]

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## Abstract [TOP](#)

**Background:** Capsular contracture remains one of the most common complications involving aesthetic and reconstructive breast surgery; however, its cause, prevention, and treatment remain to be fully elucidated. Presently, there is no accurate and reproducible pathologic in vitro or in vivo model examining capsular contracture. The purpose of this study was to establish an effective pathologic capsular contracture animal model that mimics the formation of capsular contracture response in humans.

**Methods:** New Zealand White rabbits ( $n = 32$ ) were subdivided into experimental ( $n = 16$ ) and control groups ( $n = 16$ ). Each subgroup underwent placement of smooth saline mini implants (30 cc) beneath the panniculus carnosus in the dorsal region of the back. In addition, the experimental group underwent instillation of fibrin glue into the implant pocket as a capsular contracture-inducing agent. Rabbits were euthanized from 2 to 8 weeks after the procedure. Before the animals were euthanized, each implant was serially inflated with saline and a pressure-volume curve was developed using a Stryker device to assess the degree of contracture. Representative capsule samples were collected and histologically examined. Normal and contracted human capsular tissue samples were also collected from patients undergoing breast

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implant revision and replacement procedures. Tissue samples were assessed histologically.

Results: Pressure-volume curves demonstrated a statistically significantly increased intracapsular pressure in the experimental group compared with the control group. The experimental subgroup had thicker, less transparent capsules than the control group. Histologic evaluation of the rabbit capsule was similar to that of the human capsule for the control and experimental subgroups.

Conclusions: The authors conclude that pathologic capsular contracture can be reliably induced in the rabbit. This animal model provides the framework for future investigations testing the effects of various systemic or local agents on reduction of capsular contracture.

Breast implant capsular contracture remains one of the most common complications for both aesthetic and reconstructive breast surgery. Despite the importance of this problem, the cause and treatment have remained unresolved for the past 40 years. Further complicating this problem is that there are currently no reliable in vitro or in vivo models producing capsular contracture. Various animal models have been reported in previous studies; however, most lack the ability to produce the pathologic state of contracture and, thus, correlation of proposed treatments for clinical capsular contracture are invalid in this setting.

Histologically, the human breast capsular tissue is composed of an inner layer of fibrocytes and histiocytes, which is surrounded by a thicker layer of collagen bundles arranged in a parallel array.<sup>1,2</sup> The outer layer is more vascular and is composed of loose connective tissue. Although intuitively and clinically most would consider the degree of capsule thickness to be commensurate with the severity of capsular contracture, this has never been definitively proven, and some reports have found no correlation among contamination, thickness, and clinical contracture.<sup>3</sup>

The literature is replete with earlier studies that attempted to detect differences in capsule characteristics between those formed around smooth versus textured implants. Both gross and histologic sections revealed a thicker capsule, with increased cellularity surrounding the textured implants<sup>4,5</sup>; however, other reports have produced contradictory results.<sup>6,7</sup> Equally perplexing is the incongruity between studies with animal models compared with human clinical studies.<sup>4,5,8</sup> Current data have yet to determine the exact cause for contracture and thus no completely effective prophylaxis or therapy has been developed.<sup>5-9</sup> Compounding the problem is the use of various animal models for analysis of capsular contracture when the animals themselves do not produce a pathologic capsular state.<sup>6,10,11</sup>

Furthermore, a large body of conflicting data exist on the mechanisms and various cell types involved with the formation of the host capsular contracture tissue response. As with any condition where the cause is unknown, there exists a multitude of treatment modalities offered based on anecdotal or clinically based experience. The bulk of the literature on this subject is retrospective, unblinded, uncontrolled, and rarely uses elegant scientific methodology.

The purpose of this study was to develop a pathologic, reproducible, and reliable animal model for capsular contracture that is similar to human breast capsular contracture tissue. This information can be used to help systematically determine the cause of this problem and to allow options for prevention and potential treatment of capsular contracture.

## MATERIALS AND METHODS [TOP](#)

Thirty-two New Zealand White rabbits underwent implantation with customized smooth saline mini implants (30 cc; McGhan Medical, Santa Barbara, Calif.) under an approved institutional animal care protocol. Each implant was placed in the subpanniculus carnosus plane in the dorsal back region and filled to the manufacturer's recommended 30-cc fill volume. One implant was placed per rabbit, using sterile surgical technique.

The rabbits were divided into an experimental ( $n = 16$ ) and control subgroups ( $n = 16$ ). The experimental subgroup also underwent instillation of 5 cc of fibrin glue [fibrin glue is prepared with 4 ml of rabbit cryo (Pel-Freez; Pel-Freez Biologicals, Rogers, Ark.), 500  $\mu$ l of 10% CaCl (Sigma-Tau Pharmaceuticals, Gaithersburg, Md.), 1000 units of thrombin (Monarch Pharmaceuticals, Bristol, Tenn.) in 1 ml of 50 mM TrisCl (Sigma), pH 7.4] into the implant pocket as a contracture-inducing agent. The incision was closed in two layers with subdermal 4-0 Vicryl (Ethicon, Inc., Somerville, N.J.) and 4-0 interrupted nylon suture.

Rabbits were killed at 2 or 8 weeks. Before the animals were killed, each animal was anesthetized and the dorsal back area was shaved. A small incision was made directly over the implant fill valve through skin, panniculus carnosus, and capsule. The incision traversing the capsule was sufficiently small (<3 mm) to not impede the accurate assessment of intracapsular pressure. The Stryker device was connected to the valve and opening intracapsular pressure was recorded ([Fig. 1](#)). Subsequent pressures at 2-cc increments were recorded after equilibration as the implants were overfilled. Representative capsule samples were submitted in formalin for histologic evaluation for tissue architecture and capsular thickness.



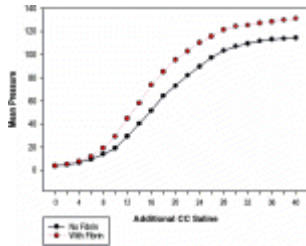
**Fig. 1.** (Above) Stryker pressure monitor setup next to the implanted mini implant. (Below) Stryker pressure monitor connected to the mini implant through a small capsular window.

Human breast capsular tissue samples from clinically normal breasts (implantation time, 6 months) and pathologically contracted capsule (Baker III/IV; implantation time, 5 to 6 months) were collected and processed using standard hematoxylin and eosin staining. The histologic sections were reviewed by a blinded pathologist and the morphologic characteristics of the human capsule samples were characterized.

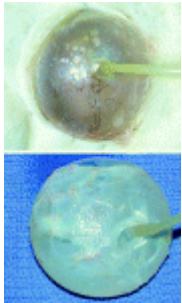
Statistics comparing the intracapsular pressures were performed using the two-tailed  $t$  test demonstrating a significant difference between the experimental and control groups. Statistical significance is defined as  $p < 0.05$ .

## RESULTS [TOP](#)

The pressure-volume curve was generated at 2 and 8 weeks ([Fig. 2](#)). There was no significant difference between the experimental and control groups at 2 weeks; however, at 8 weeks there was a significant increase in intracapsular pressure in the experimental group. On gross examination of the capsules, the control group capsule appeared more transparent and had less vessel predominance on the capsular surface ([Fig. 3, above](#)). The experimental group ([Fig. 3, below](#)) had a more opacified capsule and in many cases appeared thicker. The average capsular thickness (histologically measured) was 0.6 mm in the rabbit control group, 1.0 mm in the rabbit experimental group and in human capsules, and 2.5 mm in human capsule contractures. There was a non-statistically significant increase in capsular thickness in the experimental group.



**Fig. 2.** The pressure-volume curve at 8 weeks; there was a significant increase in intracapsular pressure in the experimental group.

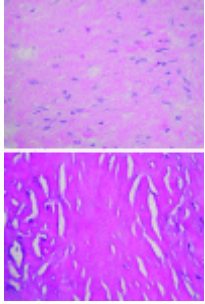


**Fig. 3.** (*Above*) Rabbit capsule at 8 weeks (control; the capsule is transparent and has less vessel predominance on the capsular surface). (*Below*) Rabbit capsule at 8 weeks (with fibrin glue); the capsule is more opacified and thicker.

## Histology [TOP](#)

Hematoxylin and eosin sections of rabbit control capsules at 8 weeks, rabbit contractures at 8 weeks, human capsules, and human contractures were compared. Synovial-like reaction of fibrohistiocytic cells (synovial metaplasia) was most pronounced in the rabbit control capsule at 8 weeks, focal in the rabbit contracture at 8 weeks, and absent in the human contractures and control capsules (which is not unexpected, as synovial metaplasia is reported to be present in only 50 percent of cases).[12](#)

Inflammation (consisting of lymphocytes, histiocytes, and eosinophils) was moderate in the 8-week rabbit control capsule and mild in the 8-week rabbit contracture. The human capsule demonstrated minimal inflammation, whereas the human contracture showed mild inflammation. The degree of fibrosis was greater in the 8-week rabbit contracture and human contracture ([Fig. 4](#)) than in their counterparts (the 8-week rabbit control and human capsules, respectively).



**Fig. 4.** (Above) Experimental group rabbit contracture at 8 weeks (original magnification,  $\times 40$ ) showing areas of more dense fibrous deposition in the mildly cellular mid zone; fibroblasts are widely separated by spindled fibroblasts. (Below) Human capsule contracture (original magnification,  $\times 40$ ) showing hypocellular fibrous mid zone; central area shows dense collagen without any fibroblasts; fibroblasts at periphery are widely separated by thick, dense bands of collagen fibers.

## DISCUSSION [TOP](#)

Capsular contracture is the most common complication involving aesthetic and reconstructive breast surgery, with a reported incidence ranging from 0.6 to 50 percent.[13,14](#) An incidence of 8 to 15 percent[15-17](#) may be cited as a more scientific appraisal. Clinically, capsular contracture manifests on a continuum with varying degrees of severity, and is typically measured subjectively by means of the Baker classification. Furthermore, contracture may become clinically evident from weeks to years after implantation.

Capsular contracture is the formation of fibrous scar tissue investing a foreign body or surgically implanted device. Artificial joints or heart valves, central venous catheter ports, breast implants, and a multitude of additional surgical devices have been involved in the development of capsule formation and its adverse consequences. Capsule formation presumably plays a vital role in the host's response to a foreign body. Nevertheless, the results of this process may pose potential serious health risks or adverse aesthetic sequelae.

The true cause of capsular contracture remains elusive.[18](#) Two prevailing theories have emerged: the *infectious hypothesis* and the *hypertrophic scar hypothesis*. The infectious hypothesis, which has been championed by Burkhardt and supported by others,[19-23](#) implicates subclinical infection in the development of capsular contracture. *Staphylococcus epidermidis*, which is the most common organism isolated from nipple secretions, is the most common organism cultured from capsules excised during open capsulotomies. Furthermore, acceleration of capsule formation around silicone implants by addition of *Staphylococcus aureus* as an independent variable has been reported.[24](#)

The hypertrophic scar hypothesis attempts to implicate noninfectious stimuli, namely, hematomas, granulomas, or hereditary factors, which confer a foreign body reaction and resultant formation of a hypertrophic scar around an implanted device. The underlying mechanism behind this process involves the activation of the myofibroblast cells within the capsule, which supposed contractile elements exert the force necessary to produce capsular contracture. Myofibroblasts contain the contractile elements actin and myosin and have been identified inconsistently within the capsules of implanted devices; however, they have proven difficult to culture and study in detail and, when found in the capsule, are found in exceedingly small quantities, are located sporadically throughout the capsule, and are not found to attach to each other. This scenario poses an inconsistent model for the development of contractile forces necessary to produce contracture.

The purpose of this study was to consider a novel pathologic animal model for capsular contracture. The fibrin glue inducing agent was discovered serendipitously in our laboratory; however, this places ample amounts of fibrinogen around the implant, and the critical role of fibrinogen in capsule formation has been scientifically established independent of our work.[25](#) This agent merely reliably produces conditions that are likely to result in a contracted capsule.

Many different animal models for contracture studies have been reported[6,8,10,19,24-28](#); however, the majority consider the effect of a given therapy on *normal* capsule formation.[6,10,11,19,29,30](#) This minimizes and likely invalidates the significance/conclusions of many of these previous studies, as therapy needs to be directed at a pathologic capsule. Other reports have used bacteria to stimulate the formation of pathologic capsules; however, the reproducibility and control of this model have not been validated.[19](#) It is our opinion that the cause of contracture is multifactorial. In humans, there exist capsular contracture-inciting agents that, for known or unknown reasons, result in a contracture (i.e., hematoma, infection). The fibrin glue inducing agent is no different. This agent simply facilitates conditions that already are known to produce capsule formation in a predictable fashion.

Furthermore, the correlation between animal contracture and that of humans has not been substantiated. In fact, several studies using the rabbit model have found contradictory results from our clinical observation in humans.[7,8](#) Most of these studies have reported more pathologic capsules in rabbits using textured implants,[4,5](#) when it is generally accepted that textured implants produce less contracture in humans. The reason for this is largely unknown; however, the use of a nonpathologic animal model is likely a major issue.

The histologic findings demonstrate a similar increase in fibrosis in rabbit and human contracted capsule compared with respective controls. The differences in synovial metaplasia in the specimens constitute a histologic detail that carries no clinicopathologic significance; however, they were reported for the sake of completeness. The end result is that the histologic analysis of the rabbit contracture model is similar to human contracture.

We report for the first time, to the best of our knowledge, a breast capsular contracture animal model that mimics the histologic characteristics of human breast capsular tissue. The degree of inflammation and fibrosis over time in the rabbit contracture appears to correlate with those of the human contracture, suggesting that the rabbit capsule may be an optimal animal model for the changes seen in human contractures. Despite these findings, we acknowledge that the ultimate model for the study of capsular contracture is the human model, and all animal models, including this one, will need to ultimately reconcile this fact.

## CONCLUSIONS [TOP](#)

Our model does produce pathologic and nonpathologic capsules histologically similar to the human pathologic and nonpathologic capsule. Interestingly, our contracture-inducing agent (fibrin) has been implicated as a key player in the formation of capsule formation in prior studies.[28](#) Plastic surgeons have endured 40 years of darkness in their true understanding of capsular contracture. We hope this model may not only provide a platform for future investigation but allow us all to see the light and provide insight into the true cause of breast implant capsular

contracture.

## ACKNOWLEDGMENTS [TOP](#)

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