Preliminary Report

CO₂-Based Tissue Expansion: A Study of Initial Performance in Ovine Subjects

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Abstract

Background: Tissue expanders are an essential reconstructive surgical tool commonly utilized in two-staged breast reconstruction. The current technology is limited primarily to saline expansion, which can be a long process requiring frequent office visits. Eliminating the need for percutaneous injections could potentially improve the psychological and physical discomfort associated with the expansion process as well as save time and resources for both the patient and surgeon.

Objectives: The authors describe a novel system of gradual, controlled, needle-free expansion. The purpose of the study was to evaluate, prior to clinical use, the in vivo communication between CO₂-based tissue expanders and their paired handheld dosage controllers and the ability of each expander to reach its intended volume.

Methods: Twelve expanders—three small (400 cm³), three medium (650 cm³), four large (850 cm³), and two full (1100 cm³)—were implanted in two mature ovines and were expanded daily with CO₂ using 12 paired handheld dosage controllers. Device performance and expansion progress (cm³/d) to size-specified volumes were observed and recorded. An on-site veterinarian monitored the animals for signs of distress during and after inflations. After full expansion of the implants, the animals were euthanized and the implants were surgically removed and examined.

Results: All 12 paired devices performed to specification, achieving successful expansion, and measured volumes of explanted expanders confirmed expansion to the labeled volume. Expansion to full volume was achieved in all units in Ovine 1 within 13 days and in Ovine 2 within 11 days. Total implantation time was 21 days in Ovine 1 and 12 days in Ovine 2. No adverse events were encountered.

Conclusions: This CO₂-based tissue expansion system offers a novel and potentially valuable tool for reconstructive surgery. This study demonstrated the in vivo performance of a CO₂-based tissue expander in an ovine model and merits future clinical research efforts. All tested devices accomplished needle-free expansion with the expanders responding to dosage-controller commands within programmed safety limitations. This system has the potential to expedite expansion through gradual, controlled distention of tissue and to simplify the process for both physician and patient.

Keywords

adjustable volume, breast reconstruction, carbon dioxide, implants, tissue expanders

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Tissue expansion is a mainstay for two-staged breast reconstruction. Although a variety of methods have been explored, the current technology for tissue expansion is limited. Studies have demonstrated the benefits of gradual, continuous expansion, but there have been no recent technological advances integrated into routine clinical practice. The most ubiquitous method for breast reconstruction typically requires frequent office visits for percutaneous saline bolus expansions, which can cause patient discomfort, involves a slow overall process, and does not provide a predictable anatomical shape.

The ideal breast tissue expander would have the following distinguishing characteristics:

- Completely implantable with no percutaneous components
- Would not require injections

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• Controllable, allowing gradual daily expansion with the ability to halt or slow the process when indicated
• Guided by patient comfort
• Easy to use
• Designed with a preformed shape emphasizing the lower pole in breast reconstruction
• Safe

Several authors have separately reported on a device developed by Osmed Gmbh (Illmenau, Germany) involving a hydrogel (vinyl pyrrolidone and methyl methacrylate) in a silicone construct that expands by osmotically absorbing local tissue fluid. The hydrogel technology meets the goals of complete implantability and gradual expansion; however, once implanted, the device expands up to 10 times its original volume without controls. Expansion begins immediately and does not allow for wound healing or adjustment for patient discomfort. Widgerow et al tested a patient-controlled expansion device comprised of an external pump connected through tubing to the implanted expander. The technology validated the safety and efficacy of gradual, patient-controlled expansion; however, the system did not achieve the goal of complete implantability, as its percutaneous tubing presented a continuous risk of contamination. The tubing and external pump also required a time-consuming setup for patients.

The search for an ideal expander ultimately requires the implantation of a device that is initially small and increases in size without percutaneous intervention. As simple as the requirement may seem, there exist only a few conceptual possibilities, including (1) a powered mechanical expansion system, (2) osmotic expansion as developed by Osmed Gmbh, or (3) the use of a compressed gas as the filling medium, with controllable release into the expander. This study addresses the latter concept using compressed CO\(_2\) as the volume medium in a tissue expander designed to meet all of the ideal expander criteria.

The objectives of this study were to validate the communication between a handheld dosage controller and its paired, surgically placed CO\(_2\) expander in an animal model and to evaluate the ability of each expander to reach its labeled volume as evidenced by visual inspection prior to explantation.

**METHODS**

**Technology**

AirXpanders, Inc. (Palo Alto, California) has developed and tested a novel, compressed CO\(_2\)-based system for controlled breast tissue expansion. The device (Figure 1) consists of an implantable expander with an outer silicone shell and an anatomically-shaped inner liner containing a small, 10-cm\(^3\) or 11-cm\(^3\) stainless steel reservoir of compressed CO\(_2\) (the size of the reservoir is associated with the size of the implant); an antenna for wireless communication; and an external handheld dosage controller.

Activated by the dosage controller, a precise dose of CO\(_2\) is released from a microscopic, flow-restricting metal tube to a solenoid-actuated valve. The microscopic tubing reduces force on the valve to a minimal level, thus lowering the power requirements necessary for valve activation. The low power requirements increase reliability and enable a major safety precaution: all power for opening the valve is located external to the implant, within the handheld dosage controller (Figure 2). The absence of an internal power source simplifies the implantable device and eliminates the risk of unintended valve activation. The valve was specifically designed with a micro-orifice with a diameter of 0.051 mm (0.002 in.), about the diameter of a human hair, to obtain both low flow and low force resulting in a gas force of 1.71 gram-force (less than the weight of a dime).

Since the AirXpander System is intended to enable patient-controlled expansion, the dosage controller is programmed with multiple safety features. The amount of released CO\(_2\) is limited for patient use to 10 cm\(^3\) per
activation and three activations per day for a 30-cm³ maximum daily dose. Once a dose is released, the system is rendered inactive for three hours, during which the patient cannot add additional volume, thus preventing overzealous expansion and potential discomfort. The dosage controller is also programmed to calculate the total volume of CO₂ contained in the expander and to limit dosing once the labeled volume is reached, preventing overfilling.

Each dosage controller permanently and exclusively bonds to one specific expander upon initial activation in the operating room. Once bonded, the controller cannot activate another expander. In bilateral cases, two controllers are used to activate and independently track the amount of CO₂ delivered to each expander. If the dosage controller is lost or damaged, a replacement can be provided and programmed for the implanted expander.

Carbon dioxide was chosen as the filling medium because of its widespread use in common medical procedures (eg, laparoscopy, intravenous imaging, cardiac surgery for prevention of air emboli and subcutaneous body sculpting). CO₂ gas insufflation is preferred by most laparoscopic surgeons because it has a high diffusion coefficient and is a normal metabolic end-product rapidly cleared from the body. CO₂ is also highly soluble in blood, significantly reducing any risk of gas embolism, and it does not support combustion.

In the unlikely event of a valve failure resulting in a wide-open valve, the total volume of CO₂ (maximum of 2.2 liters) would be released from the reservoir into the inner gas barrier through the valve orifice in approximately four minutes. This could lead to pain, wound dehiscence (dependent on the healing stage of the surgical site), and/or implant rupture requiring device replacement. Wound dehiscence with implant exposure, device rupture, and device replacement are rare but have been reported in the literature.

Rudston-Brown et al reported the effects of 6-L and 12-L subcutaneous CO₂ insufflations on arterial pCO₂ in anesthetized juvenile pigs in an effort to determine whether PaCO₂ and arterial pH were elevated following intentional insufflation of CO₂ into the subcutaneous space and to determine the length of time for which the effects remain significant. Their study is important to ours as it addresses the physiological effects of CO₂ release into the subcutaneous space. The amount of CO₂ in Rudston-Brown et al’s study was three-to-six times the amount that could be released from the CO₂-based tissue expanders. The authors’ model represents “the worst case scenario where a patient who has severe chronic obstructive lung disease could develop a respiratory acidosis from subcutaneous emphysema following laparoscopic surgery.” Measurements of arterial blood gases were recorded every five or 10 minutes, and PaCO₂ and arterial pH took approximately 100 minutes to return to baseline after insufflation with both 6-L and 12-L volumes. CO₂ subcutaneous insufflation volumes of less than 6 L were not associated with elevation in PaCO₂.

Assuming a 50-kg patient weight, the maximum amount of CO₂ that could be released from a full AirXpander reservoir (2.2 L) is 44 mL/kg, compared with 220 mL/kg in the 6-L insufflations and 440 mL/kg in the 12-L insufflations in the Rudston-Brown et al study. Based on this study, the absorption of 2.2 L of CO₂ would not result in clinically significant hypercapnea or respiratory acidosis. It is expected that any CO₂ released into the surgical pocket would be absorbed by the surrounding tissue into the bloodstream and eliminated through the normal gas exchange process via the lungs.

Because of the high diffusion coefficient of CO₂, the AirXpander System includes an inner liner that is designed to contain the CO₂ and to minimize loss from permeation. The internal liner is also anatomically shaped and nondis tendable at full volume, thus maintaining its anatomical shape with lower pole emphasis even under resistance in the surgical pocket. The expander comes in four sizes, the dimensions of which were developed to match the permanent breast implants that would likely succeed the expander in the reconstructive process.

**Experimental Methods**

The 12 investigational tissue expanders used in this study underwent extensive bench testing consisting of product performance with cycle, impact, and burst limit testing; permeability testing; and biocompatibility and sterility in accordance with US Food and Drug Administration (FDA) Good Manufacturing Practices and International Organization for Standardization (ISO) recommendations. In an early animal study, expanders were placed in one ovine. The energy initially transmitted from the dosage controller was insufficient to hold the valve open long enough for delivery of a full dose of CO₂. Consequently, the transmission energy was increased, and the device was retested in a second sheep with resolution of the problem. It was from these modified devices that the present study devices were developed.

For this trial, the principal investigator selected three small (400 cm³), three medium (650 cm³), four large (850 cm³), and two full (1100 cm³) expanders, for a total of 12 expanders. These were implanted dorsally in two male ovines (Ovine 1, 98.0 kg; Ovine 2, 89.6 kg) (Figure 3). The ovine model was chosen over other large animals (such as a porcine model) because of the ovin’s clean habits, sedate nature, and reluctance to roll on its side or back. Placement of the sizes was random, with the exception of the left and right back locations, which were more suitable for the small (400 cm³) and medium (650 cm³) expanders. The pelvic bones of sheep are directly below the back locations and, with an ambulatory animal, tend to bias implants upward toward the skin surface, putting additional stress on the radial access incisions. The study was conducted at LyChron (Mountain View, California) in accordance with the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) animal care guidelines from February 2009 to March 2009.

Preoperatively—after the animals were shaved, scrubbed, and aseptically prepared on the dorsal thoracic and lumbar regions—the surgical area was infiltrated with 0.5% lidocaine...
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Surgical dissection was accomplished by three transverse incisions over the dorsal midline, thus providing radial approaches for dissection of bilateral paraspinal pockets in the subcutaneous plane. After implantation, bonding between the 12 dosage controllers and the 12 expanders was established and confirmed based on audible and visual signals from the controllers. Prior to closure, weak signals were identified from two of the implants, which necessitated adjustment of the expanders (much like adjusting folds in current saline implants); this improved the strength of the signals. The skin was closed with 2-0 Vicryl (Ethicon, Inc., Somerville, New Jersey) and 35 W staples. Intraoperative inflation was performed for each implant to fill the dissected pockets with 84 to 394 cm³ CO₂, based on the expander size.

Beginning on Postoperative Day 1, the implants were expanded by 10% (40-110 cm³/d) for up to 13 days based on implant size (Figure 4). Dosing was confirmed by the audible and visual signals from the controller and visual assessment of inflation. The on-site veterinarian observed the animals for signs of pain or discomfort (excessive scratching, anorexia, or lethargy) during and after inflation. The inflation process for each expander was halted once full volume was observed, and photographs were taken (Figure 5). Ovine 1 was observed for an additional seven days after reaching full expansion to confirm maintenance of labeled volume and to evaluate a safety feature that prevents overfilling once full expansion has been achieved. The subject animal was euthanized with removal of the expanders on Day 21.

Prior to euthanizing Ovine 2 on Day 12, two implants were selected for additional testing. With the animal sedated, the left back (small, 400 cm³) expander was vented with a 22-gauge needle to observe percutaneous deflation of the implant. The right front (large, 850 cm³) expander was selected to simulate rupture of the implant with release of subcutaneous CO₂. A specifically programmed key (not supplied with the system) was inserted into the dosage controller to suppress the preset limits, thus allowing the investigator to fill the implant beyond its labeled volume. Over a period of eight minutes, the implant was filled to 189% of its labeled volume, resulting in a gradual release of CO₂ into the subcutaneous pocket.

RESULTS

All 12 expanders responded to their corresponding dosage controllers as confirmed by audible and visual signals, postexplantation volume measurements, and analysis of the dosage tracking data. Six implants expanded successfully by Day 13 in Ovine 1 (Figure 5), and the other six expanded successfully by Day 11 in Ovine 2. Additionally, the ability to maintain full expansion was confirmed in Ovine 1 for seven days following completed expansion. The dosage controller software prevented overfilling of the expanders by limiting additional dosing once the calculated maximum volumes were reached. Fill volume data downloaded from the dosage controller are shown in Figure 6. Postexplantation analysis of actual final volumes confirmed that the expanders met the specifications for their labeled volumes. The left back (650 cm³) expander in Ovine 1 and the right back (650 cm³) expander in Ovine 2 exhibited the largest variance—13%
and 20%, respectively—below their labeled volumes. This may have been due to the pressure exerted in this area by the ambulation of the animal subject (Table 1).

Needle venting of an implant to simulate percutaneous deflation was effective with a 22-gauge needle. Intentional overfilling beyond the volume limits demonstrated compromise of the inner liner with a slow release of CO₂ into the subcutaneous pocket, without observed adverse effect to the animal (Figure 7). Postexplantation analysis of the compromised expander demonstrated an expected slight separation at the seam of the inner liner.

All implants performed to specification, and gradual daily expansion was achieved. At no time did either animal demonstrate distress (anorexia, excessive scratching, and/or lethargy) with the tissue expansion process, and no adverse safety events or device failures were identified.

**DISCUSSION**

Tissue expansion is a well-established technique and a key component of breast reconstruction. In the present study, we did not intend to elucidate the science of tissue expansion. Rather, the animal study sought to determine whether a new CO₂-based system could optimize the process of tissue expansion based on existing science and whether proceeding with clinical testing was warranted. We also sought to identify any iterative design changes that might further improve the clinical procedure, outcomes, or patient experience.

The CO₂-based tissue expansion system tested in the study meets the criteria outlined earlier in defining the ideal expander technology. The system is completely implantable, offers the capability for gradual controlled expansion without percutaneous components or injections, and (based on the results of the study) is easy to use. The AirXpander System provides a method of rapid expansion, which theoretically could lead to earlier permanent implant exchange. A needle-free tissue expander may also reduce patient anxiety and the risk of percutaneous transmitted infection.

Tissue expansion with the described system is anticipated to take approximately three to four months: two to three weeks from placement of the implant to beginning

Table 1. Comparison of Measured, Postexpansion Volumes of Tissue Expanders After Removal From Ovine Subjects With Corresponding Labeled Volumes

<table>
<thead>
<tr>
<th>Ovine #</th>
<th>Implant Location</th>
<th>Labeled Volume, cm³</th>
<th>Measured Volume, cm³</th>
<th>% Change</th>
<th>Product Specification, %</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Left front</td>
<td>850</td>
<td>830</td>
<td>-2</td>
<td>±20</td>
<td>Pass</td>
</tr>
<tr>
<td></td>
<td>Left middle</td>
<td>850</td>
<td>858</td>
<td>1</td>
<td>±20</td>
<td>Pass</td>
</tr>
<tr>
<td></td>
<td>Left back</td>
<td>650</td>
<td>519</td>
<td>-20</td>
<td>±20</td>
<td>Pass</td>
</tr>
<tr>
<td></td>
<td>Right front</td>
<td>400</td>
<td>414</td>
<td>4</td>
<td>±20</td>
<td>Pass</td>
</tr>
<tr>
<td></td>
<td>Right middle</td>
<td>1100</td>
<td>1030</td>
<td>-6</td>
<td>±20</td>
<td>Pass</td>
</tr>
<tr>
<td></td>
<td>Right back</td>
<td>400</td>
<td>392</td>
<td>-2</td>
<td>±20</td>
<td>Pass</td>
</tr>
<tr>
<td>2</td>
<td>Left front</td>
<td>650</td>
<td>674</td>
<td>4</td>
<td>±20</td>
<td>Pass</td>
</tr>
<tr>
<td></td>
<td>Left middle</td>
<td>1100</td>
<td>1189</td>
<td>8</td>
<td>±20</td>
<td>Pass</td>
</tr>
<tr>
<td></td>
<td>Left back</td>
<td>400 Vented device</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Right front</td>
<td>850 Vented device</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Right middle</td>
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<td>868</td>
<td>2</td>
<td>±20</td>
<td>Pass</td>
</tr>
<tr>
<td></td>
<td>Right back</td>
<td>650</td>
<td>566</td>
<td>-13</td>
<td>±20</td>
<td>Pass</td>
</tr>
</tbody>
</table>

NA, not applicable.

![Figure 5. Fully expanded implants.](image-url)
of expansion, followed by two to three weeks of expansion, and then approximately four to eight weeks until explantation of the expander and placement of the permanent implant. The present system is designed for patient-controlled daily expansion. Thus, this system could obviate the frequent office visits required for saline expansion along with the associated resources, such as office staff and consumables. The predetermined, lower pole projection of the expander in the study was maintained, as the anatomically-shaped inner liner is not distensible at full volume.

One of the limitations of a CO\textsubscript{2}-based tissue expansion system is potential unintended CO\textsubscript{2} expansion due to acute altitude changes; patients in ascending aircrafts or rapidly ascending (> 1000 meters) ground-based transport are likely to experience changes in the relative internal pressure of the expander. The current study does not address tissue compliance in such settings, and therefore initial clinical trials should limit abrupt altitude changes in implanted patients. The current tissue expander has no means for removing CO\textsubscript{2} from the implant without permanently disabling the device. For this reason, caution is advised to prevent filling of the expanders beyond the comfort level of the patient or the tolerance of the tissue. Additionally, a paucity of biological research exists for radiation therapy with any breast expander device, and studies are necessary to elucidate the potential compatibility of the AirXpander device in situations for which postoperative pathology results indicate chest wall irradiation. Because the CO\textsubscript{2} reservoir is constructed of stainless steel and the effect of the reservoir on a radiation beam has not been tested, implantation with the AirXpander System—as well as with traditional integrated-port systems—is not indicated in patients requiring concurrent radiation therapy.

**CONCLUSIONS**

CO\textsubscript{2}-based tissue expansion offers a new approach for an important reconstructive surgical tool. This study demonstrated the in vivo performance of such a system in an ovine model, establishing that it can be used effectively and safely to achieve tissue expansion. Based on the positive results of the animal study, clinical studies are indicated to confirm safety and performance when the device is placed for reconstructive surgery in current practice. Additionally, although the expanders are designed for breast reconstruction, the advent of a needle-free and gradual expansion technology calls for studies of other potential indications, such as those in pediatrics, burns, and trauma reconstruction.
Disclosures

Dr. Jacobs is a paid employee (Chief Medical Officer) and shareholder at AirXpanders, Inc. (Palo Alto, California), the manufacturer of the product discussed in this study. Mr. Jones is a private consultant and shareholder at AirXpanders. Dr. Menard is a paid member of the scientific advisory board and holds stock options with AirXpanders, Inc.

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The sponsor of the study, AirXpanders, Inc., supported the costs of the laboratory materials, monitoring and care of the animals, and operating room expenses. Dr. Menard, a paid member of the scientific advisory board of AirXpanders, Inc., received a small stipend for the preparation of the manuscript. A medical writer was hired to edit and format the manuscript.

REFERENCES