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Pneumatic delivery of untethered microgrippers for minimally invasive biopsy

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Abstract

The surgical biopsy is one of the most widely utilized medical procedures for diagnosis of a number of diseases. In order to enable less invasive biopsies, we have previously developed and applied residual stress and physiologically activated sub-millimeter sized untethered grippers. Here, we report a controlled, pneumatic system and methodology for pressurized delivery of untethered microgrippers (μ-grippers) to improve the efficacy of tissue excision. The approach is compatible with current minimally invasive laparoscopic and endoscopic methods. Using a model experimental system, we observed that pneumatic delivery significantly improves the efficiency of the tissue attachment—μ-grippers attach up to 30-fold better on vertically oriented tissues, and up to 3.5-fold better on horizontally oriented tissues as compared to experiments without pressurized delivery. Hence, the use of pneumatics in the delivery of untethered microdevices could significantly enhance their efficiency in minimally invasive biopsy procedures.

I. INTRODUCTION

As the next frontier in minimally invasive surgery, the use of untethered microdevices promises to make a variety of procedures such as drug delivery, robotics or biopsy less invasive and more efficient [1–3]. In many procedures such as biopsy, after the introduction of microdevices using endoscopic techniques, it is imperative that these devices reach and secure themselves firmly on the tissue surface, but this can be challenging due to the small size of these devices, fluid flow, and the mucus lining. In the absence of any wires, tethers or batteries, magnetic fields can be used to direct these devices, but such guidance procedures can be challenging to implement in three dimensions and in a clinical setting. In this paper, we investigate the use of pneumatics to direct the microdevices and improve the previously reported performance of the μ-grippers. Previously these grippers were used to biopsy gastrointestinal organs in live pigs [4,5]. While these studies demonstrated viability of the approach by retrieving high quality tissue, cell, and genetic samples, the further development of the approach requires a robust and uniform delivery of the μ-grippers to the mucosa, which is the focus of the current work.

In prior in-vivo studies, the tissue excision efficiency was reduced to some extent because some of the μ-grippers were washed away and were unable to attach securely to the tissue

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surface. Here, inspired by previous studies on pressurized delivery of liquids for transdermal drug delivery [6], we investigate the use of pneumatic mechanisms to dispense the μ-grippers with external force so that they can reach and attach to the tissue surface more securely and consequently overcome the aforementioned limitations for biopsy applications.

II. EXPERIMENTS

A. Fabrication of μ-grippers

The composition and fabrication process flow of the μ-grippers are described in detail in previous papers [4, 7]. Briefly, they are composed of a human finger-like segmented design, with rigid gold coated nickel segments separated by thin flexible chromium / gold / polymer or wax hinges. The polymer or wax acts as the thermally responsive trigger so that at cold temperatures the gripper remains open and only closes when the trigger is softened, dissolved or delaminated. The energy / force required to close the μ-grippers is derived by the release of residual stress in the chromium thin film patterned within the hinges. The attractive feature of this approach is that untethered autonomous actuation can be enabled *en masse* under physiological conditions. For the microgippers used in this paper, the hinges were designed to trigger at 37°C.

Figure 1 shows autonomous actuation of the μ-grippers and the grabbing action of a single gripper. The μ-grippers are fabricated in a highly parallel manner. As many as thousands can be patterned on a single 4-inch wafer, with sizes ranging from 100 microns to 1 mm. It is noteworthy that present day biopsy forceps are much larger. The μ-grippers can be made small enough to fit in present day endoscopic catheters and can be introduced via syringe during a typical endoscopic procedure. It is important that any advancement in deployment of these μ-grippers be compatible with modern day endoscopy for convenient integration.

B. Pneumatic delivery system compatible with endoscopic catheters.

The pneumatic device used in our experiments was the MFCS-100 microfluidic flow control system from Fluigent. An approximately 150 psi air gas line was connected to the rear of the main MFCS-100 system. A computer connected to the MFCS-100 controlled the pressure released in the front of the device. The pressurized gas release was connected to a liquid vial and a bolus of liquid was released using a computer controlled switch. In our experiments, the μ-grippers were loaded into a vial containing liquid and were released along with the liquid bolus onto the target through a catheter made of polyetheretherketone (PEEK) as shown in Figure 2. In a clinical setting, this catheter can be inserted through one of the instrument channels of the endoscope.

The μ-grippers endure a turbulent environment during their transport from the vial to the end of the catheter which includes sudden pressure drops and sharp directional changes. This rough transport damages a small fraction of the μ-grippers. To determine the relationship between applied pressure and the fraction of damaged μ-grippers, a break test was carried out. In this experiment, μ-grippers were dispersed into clear well plates at pressures of 3, 10, 15, 20, and 30 psi, with the end of the outlet tubing submerged in water. The μ-grippers were then imaged with an optical microscope to discern any breakage. The results are shown in

Figure 3 and indicate that even at low pressures of 3 psi there is some breakage which is attributed to the pressurization of the loading vial which forces the liquid level of the vial down and into the outlet tubing with much agitation. On the other hand, even at pressures as high as 15 psi, 50% of the μ-grippers are still viable. We estimate that 10 psi is the maximum level of pressure for the current delivery system which represents a trade-off between biopsy effectiveness and μ-gripper viability. It is also possible to further reduce the damage to the μ-grippers by employing alternate pneumatic-microfluidic interfaces.

The attachment of the μ-grippers was assayed by dispersing them on tissue in two different configurations. The tissue was either submerged in a horizontal orientation, or a vertical orientation in air to simulate the various angles and conditions that might be encountered during dispersion within the gastrointestinal tract (Figure 4). These choices were based on applications of dispersal on the esophageal wall vs colon wall. After dispersal at different pressures, the attachment was assayed by flowing water using the Harvard Apparatus PHD Ultra™ infuse pump at flow rates of 19 mL/min estimated to be about 480 times the flow rate of mucus in the gastrointestinal tract of 5 mm/min [8–10].

The relative position of the μ-grippers on the tissue was measured before and after flow (Figure 5). We observed significantly higher attachment, measured by resistance to detachment during flow with pneumatic release (Figure 6). Even at low pressures, in going from 0 to 1.5 psi, there was a significant increase in attachment as high as a 26% difference. On vertically oriented tissue too, we observed statistically significant increase of attachment but with larger statistical variation (Figures 7, 8).

The pressure used for pneumatic delivery can be converted to a velocity by utilizing the Hagen-Poiseuille equation and using the dimensions of the tubing and flow rate [11]. Using this approach, we estimate that the velocity is in the range of 0 to 60 m/sec over the pressure range investigated which is smaller than the velocities used for transdermal delivery of particles. Additionally, the diameter of the μ-gripper delivery tube is small, which reduces both tissue damage and the possibility of tissue puncture. Nevertheless, we have seen a significant improvement in attachment and it is important to note that the process implemented is compatible with endoscopy and dispersal through catheters.

III. CONCLUSION

An emerging area for small medical robots are untethered devices, often dispersed in large numbers. Previously, we showed how residual stress responsive μ-grippers could be used to biopsy tissue. Here, we provide convincing evidence that the delivery of these devices through catheters using a pneumatic dispersal approach could significantly improve attachment. Since the μ-grippers need to attach to the tissue surface in order to collect cell samples, our results suggest that the increase in the percent attachment would lead to more efficient biopsy procedures. Furthermore, this pneumatic method is also suitable for deployment of alternate micro and nanoparticle untethered devices when self-locomotion or magnetic propulsion is unavailable.

Acknowledgments

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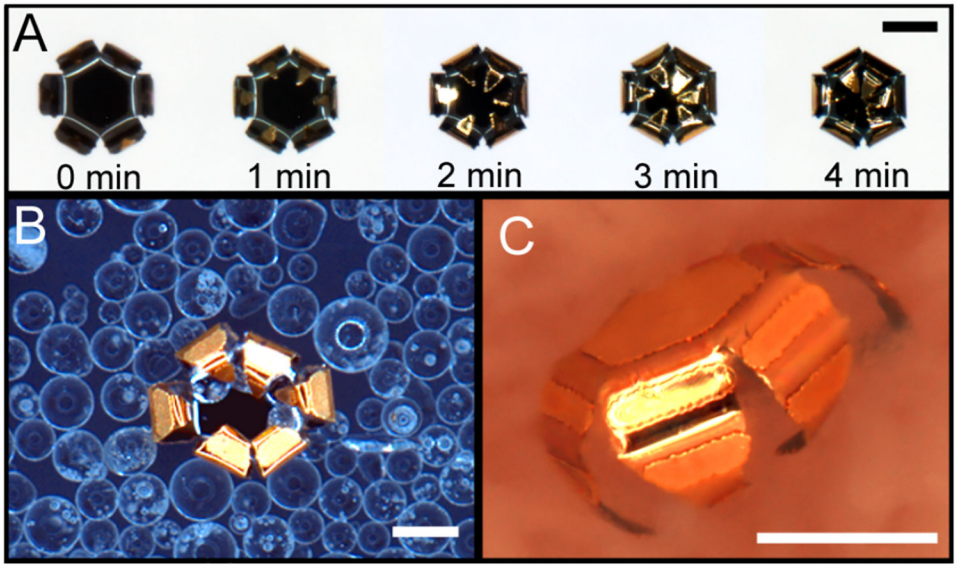


Fig. 1.

Optical images of the thermo-sensitive μ-grippers. (A) Time-lapse images of a μ-gripper closing in water at 37°C. (B) Optical image of a μ-gripper closing and gripping three glass beads. (C) Optical image of a μ-gripper closed on pig stomach tissue, ex-vivo. The scale bars represent 200 μm.

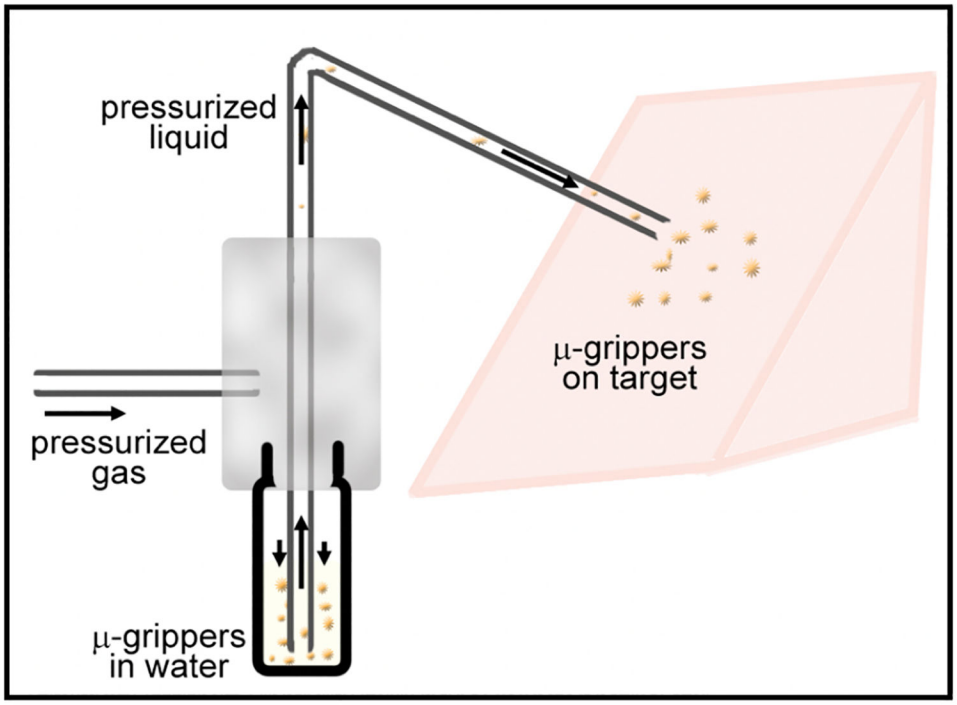


Fig. 2. Schematic representation of the pneumatic μ-gripper delivery approach.
Pressurized gas is used to send a bolus of liquid containing μ-grippers onto the tissue.

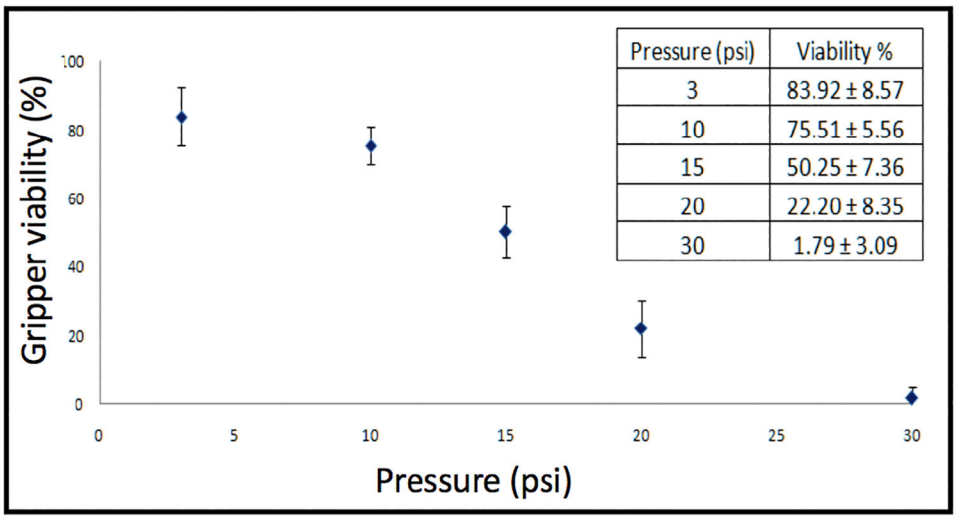


Fig. 3. Average viability of the μ-grippers after pneumatic release using our integrated system at different pressures.

Viability is defined as the percentage of the μ-grippers that are unbroken after exit from the tube.

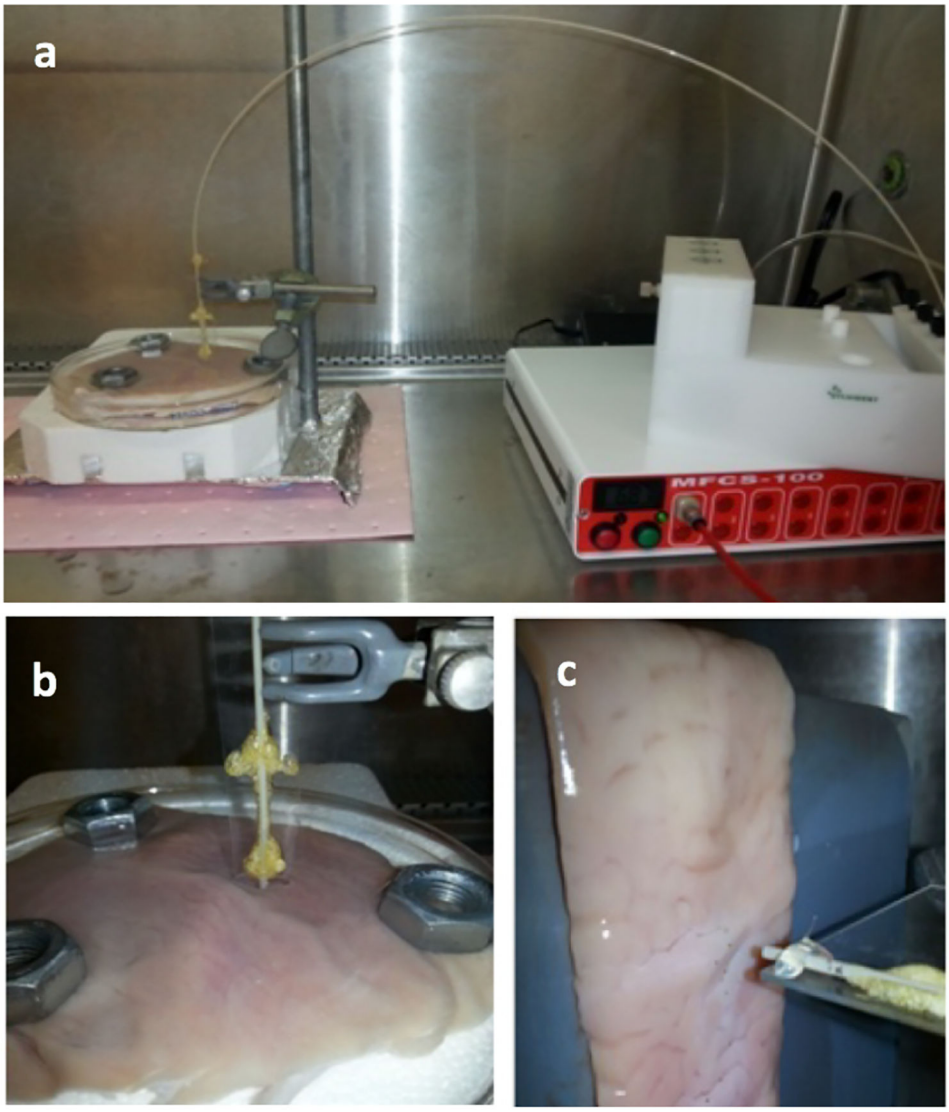


Fig. 4. Optical images showing pneumatic dispersal of μ-grippers on tissue in two configurations.
(a) Image of set up with pneumatic dispensation unit and delivery in (b) horizontal and (c) vertical configurations.

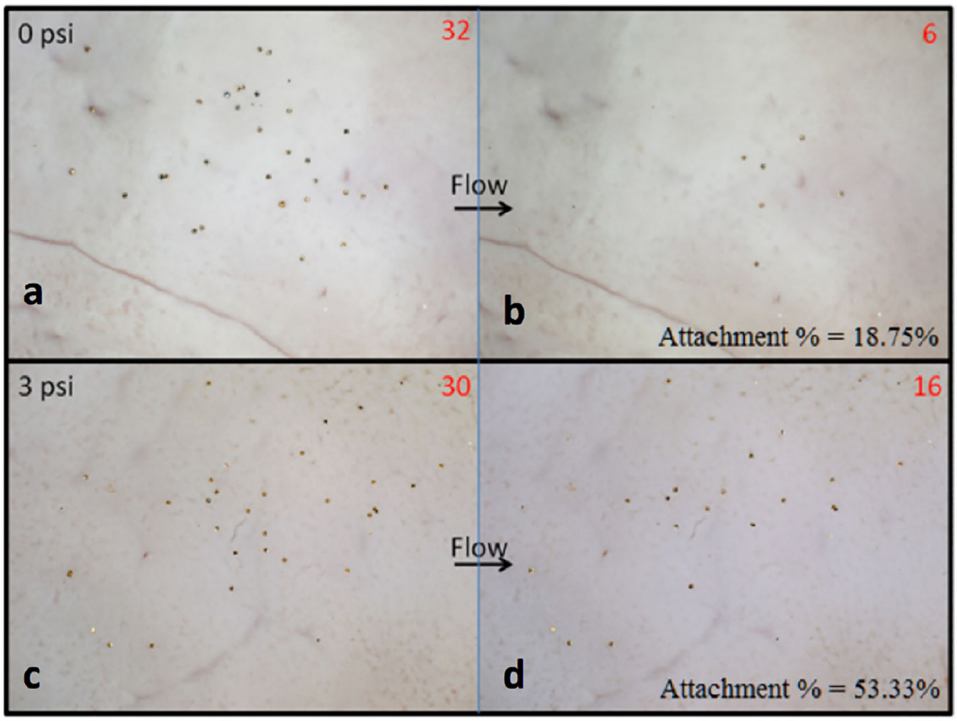
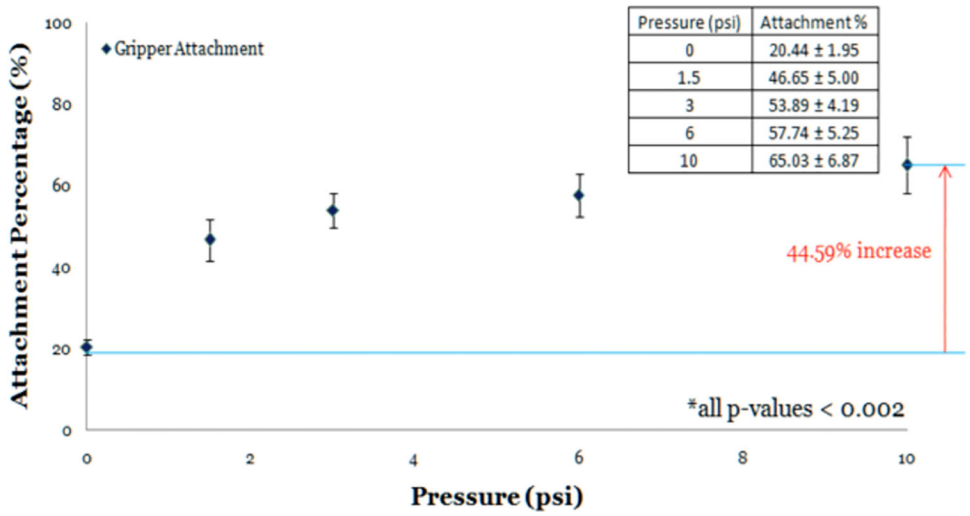


Fig. 5.

Optical images of μ-grippers on tissue after pneumatic delivery at two pressures (a, b) 0 and (c, d) 3 psi; (a, c) before and (b, d) after flow.



Pressure (psi)	Attachment %
0	20.44 ± 1.95
1.5	46.65 ± 5.00
3	53.89 ± 4.19
6	57.74 ± 5.25
10	65.03 ± 6.87

Fig. 6. Graph of attachment percentage vs pressure used for pneumatic delivery on horizontally oriented tissue.

Results show a significant increase in attachment percentage with increasing pressure.

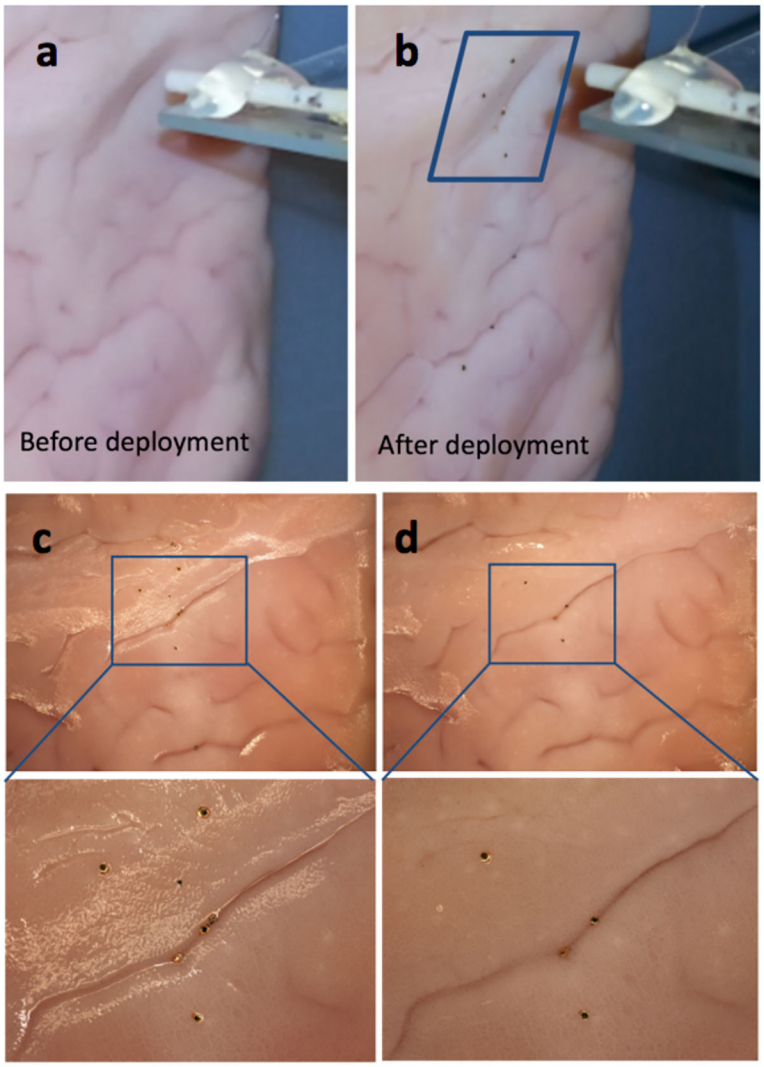


Fig. 7. Optical images of the μ-grippers pneumatically dispensed on vertically oriented tissue.
(a-b) Optical image showing the tissue target before and after μ-gripper pressurized dispensation at 8 psi. (c-d) Progressive zoomed in image of the sample before and after flow showing that some μ-grippers were dislodged after flow.

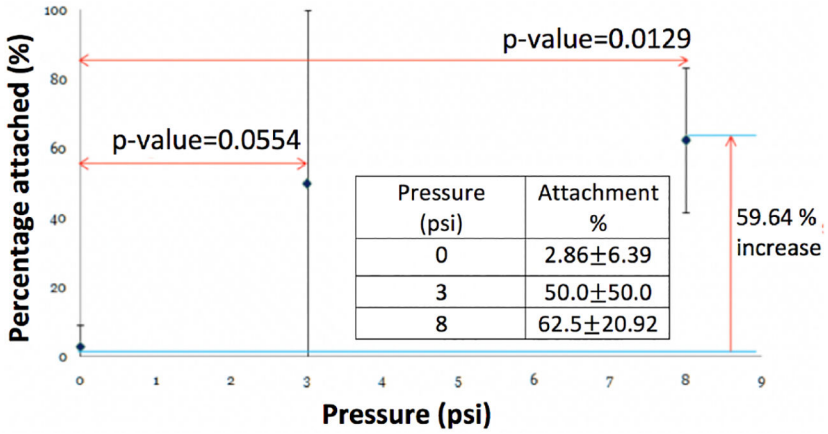


Fig. 8. Graph of the attachment percentage vs pressure used for pneumatic delivery on vertically oriented tissue.

The results indicate a statistically significant increase in the attachment percentage at pressures of 3 and 8 psi as compared to no pressure.