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Minimally Invasive Surgery via Laparoscopy for Intra-Abdominal Biopsy in Obese Rhesus Macaques (*Macaca mulatta*)

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Purpose. **To determine the safety and effectiveness of laparoscopy for repeated intra-abdominal biopsy of liver and omental adipose tissue (AT) in obese rhesus monkeys *(Macaca mulatta)*.**

Methods. **Nine obese rhesus monkeys were studied by use of 18 laparoscopic procedures (two procedures each, approx. six weeks apart). Time-sensitive liver and omental AT specimens were obtained from monkeys under general anesthesia, using a three-port approach with a roticulating endoscopic stapler/divider and a monopolar electrosurgery for hemostasis.**

Results. **All subjects tolerated the initial and repeat laparoscopic procedures well. Liver specimens weighed a mean ± SEM of 3.8 ± 0.5 g, and omental AT specimens weighed 16.6 ± 0.8 g. Compared with previous studies of conventional laparotomy with liver wedge resection, the monkeys experienced faster postoperative recovery via laparoscopy, with rapid return to normal food intake and activity. Minimal to no adhesions were observed by use of the repeat procedure in all monkeys, with no major complications.**

Conclusions. **Laparoscopy in obese rhesus monkey (ranging from young to older-aged), with repeated intra-abdominal liver and omental AT biopsy, was an excellent minimally invasive surgical method. In contrast to laparotomy with wedge resection, this approach greatly decreases operative time and stress, provides generous tissue specimens in a time-efficient manner, and facilitates rapid and full recovery of the nonhuman primate.**

Nonhuman primates are thought to be among the oldest recorded animal models for scientific research (20). Among Old World monkeys, the rhesus monkey (*Macaca mulatta*) was among the four most-cited species in research publications (13). Over several decades, the rhesus monkey has proven to be a unique and valuable research model due to its close physiologic and metabolic similarity to humans.

Previous studies in our laboratory have documented the remarkable similarity of the middle- and older-aged rhesus monkey to humans in the spontaneous development of obesity (22), hypertension (2), dyslipidemia (1, 16, 26, 36), insulin resistance (3, 4), type-2 diabetes mellitus (17, 18, 28, 29), and related complications (8, 10, 33, 35).

Recent estimates have cited epidemic proportions of obesity, the metabolic syndrome X, prediabetes, and type-2 diabetes in the United States. Clearly these disorders represent a major health crisis in need of well-defined therapeutic intervention. However, much remains unknown about these conditions regarding the causative pathophysiologic mechanism(s), underlying defects, and possible therapies.

Newly developed biochemical and molecular techniques have fostered great interest in specific organ- and tissue-related changes concurrent with the in vivo changes signaling the onset and progression of obesity, type-2 diabetes, and related conditions. The obese rhesus primate is an excellent model with which to undertake such studies, as it is suitable for repeated experimental blood sample collection and accompanying tissue biopsy.

Muscle and adipose tissue (AT) sampling in the obese and diabetic rhesus monkey has been well-documented (27-29). In addition, contributions from the study of hepatic and AT regarding the transitional pathologic changes and eventual development of type-2 diabetes are of great interest. Muscle and subcutaneous fat biopsy specimens are obtainable without invasive surgical procedures, but safe and efficient access to liver and omental AT in the primate model can be problematic. Simultaneous biopsy of metabolically active tissue (e.g., muscle, subcutaneous AT, omental AT, and liver) and evaluation of gene expression are increasingly important in examination of the relative role of each component in the development of the pathophysiologic mechanism(s) (27, 30).

In the past, the ability to obtain intra-abdominal liver biopsy specimens from primates was limited to an open surgical approach via laparotomy (27, 30). Similar to that in humans, laparotomy is a major surgical procedure which, in the large, obese rhesus monkey, requires general anesthesia (in our experience with obese primates), sometimes requiring partial neuroleptic paralysis, two-hour or longer operative time (depending on any complications), major tissue and incisional healing, and lengthy postoperative recovery. In some institutions, repeated survival laparotomy is not advisable in primates in periods of less than six to 12 months. Additionally in some institutions, laparotomy is a major surgical procedure, and may not be permissible more than two times during a single protocol (25).

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In contrast, the technique of laparoscopy from its earliest development, as reviewed in Dukelow (12) and Harrison (19), as well as specific reports of laparoscopy and the study of reproductive function in the rhesus monkey (11) and in the chimpanzee (15), support use of this approach. Specifically, the laparoscopic technique allows frequent observation of internal tissues without the trauma of a major surgical procedure (12). In addition, the stress for the primate is minimal, there is opportunity for repeated procedures, and postoperative recovery is rapid and uncomplicated.

The laparoscopic technique has been adapted for wide use in zoological medicine (7), and is performed in baboons for liver and spleen biopsy (9, 32), in rhesus monkeys for performing serial kidney, spleen, small intestine, and lymph node biopsies in human immunodeficiency virus (HIV) studies (31), and in rhesus monkeys for the study of hepatectomy and liver regeneration (14).

Therefore, we sought to establish a minimally invasive surgical approach, using laparoscopy for repeat intra-abdominal tissue sampling, in our obese rhesus monkeys that ranged from young, to middle- and older-aged. The challenge of the study reported here was to carry out the laparoscopic technique in high-risk primates, obtain time-sensitive liver and omental AT, and achieve rapid postoperative recovery with minimal or no complications, so that the laparoscopy and tissue sampling could be repeated in six weeks under identical conditions.

Materials and Methods

Subjects. Nine male obese rhesus (*Macaca mulatta*) monkeys were studied, and ranged in age from 8.5 to 20.3 (mean ± SEM: 14.6 ± 1.8) years and in body weight from 11.6 to 19.6 (15.4 ± 0.9) kg. The monkeys were obtained from primate centers and suppliers in the United States. Viral status was not specifically determined. The monkeys were individually housed under well-controlled environmental conditions, with room temperature maintained at 22°C and light/dark cycling at 6 a.m. and 6 p.m. daily. The primates were provided with standard primate chow ad libitum (PMI Nutrition International, LLC, Brentwood, Mo.), free access to fresh water, and a chewable multi-vitamin daily. All protocols were in accord with the National Institutes of Health *Guide for the Care and Use of Laboratory Animals* (25), and were approved by the University of Maryland Institutional Animal Care and Use Committee.

Preoperative care and anesthesia. After a 16-h overnight fast, the monkeys were sedated with ketamine hydrochloride (15 mg/kg of body weight given intramuscularly). Atropine (0.4 mg/kg subcutaneously) was given to reduce respiratory tract secretions. Baseline and ongoing vital signs (systolic and diastolic indirect blood pressures, pulse, and mean arterial pressure) were obtained, using a Critikon-Dinamap Veterinary Blood Pressure Monitor 8300 (Tampa, Fla.). Preoperative aseptic preparation of the abdominal area was carried out, including shaving of hair and preliminary surgical scrub of the skin with 2% chlorhexidine (Fort Dodge, Fort Dodge, Iowa) and alcohol. A peripheral venous catheter was inserted for administration of replacement fluids (lactated Ringers' solution; 10 ml/kg/h). Monkeys were positioned supine with cardio-respiratory monitoring equipment, including a capnograph monitor (Criticare Systems, Inc., Waukesha, Wis.) for continuous assessment of end-tidal CO_2 concentration, pulse oximetry, and respiratory pattern and rate, and for continuous monitoring of the ECG pattern and rate (VetSpecs 9061V, Franklin, Wis.). A Salem nasogastric tube (Bard, Covington, Ga.) was used to decompress the stomach and remove residual stomach contents, if any. Intubation was accomplished using intravenously administered sodium pentothal (5 to 7 mg/kg in half-dose increments, given to effect) or isoflurane by mask (flow rate of 2.5 to 3.0%, with 2% oxygen). Lidocaine (2%) with epinephrine (1:100,000) solution was administered topically to facilitate intubation. Anesthesia was maintained with isoflurane (0.75 to 1.5%).

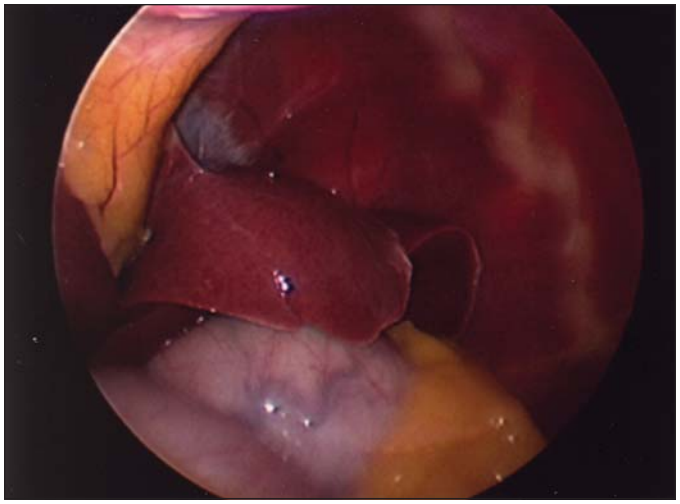

Figure 1. Laparoscopic view of left lobes of the nonhuman primate liver.

Laparoscopic retrieval of specimens. A grounding pad and conducting gel (Conmed Corporation, Utica, N.Y.) was placed under a shaved hair area of the monkey's back. The skin over the abdomen was prepared with chlorhexidine scrub and alcohol, and the abdominal area was draped, using aseptic technique. The instruments, including a laparoscopic irrigation and suction set (Bard, Cranston, R.I.), endoscopic camera, light cord, and carbon dioxide (CO_2) insufflation tubing (Stryker Endoscopy, San Jose, Calif.), and an endoscopic monopolar coagulator (Floating Ball, TissueLink Medical, Dover, N.H.), were passed onto the field.

Three access ports were used for biopsy of the liver and omental AT. Initial access was obtained through a five-millimeter-long midline incision two to three centimeters anterior to the umbilicus, through which a disposable pneumoperitoneum needle (Veres needle; Surgineedle; U.S. Surgical, Norwalk, Conn.) was passed into the abdomen, using closed technique. A saline drop test was used to confirm placement of the tip into the free intraperitoneal space.

Pneumoperitoneum was created, using CO_2 insufflation with a high-flow insufflator, to a pressure of eight to 12 mmHg. Next, a five-millimeter-diameter trocar (Ethicon, Inc., Somerville, N.J.) was placed, using closed technique, and a five-millimeter-diameter, 30 degree-angled laparoscope (Stryker Endoscopy, San Jose, Calif.) was passed into the abdomen. Exploratory laparoscopy was performed to evaluate the feasibility of laparoscopic liver biopsy, as well as to evaluate for injury to the viscera during initial peritoneal access (Fig. 1). The surgical table was set in reverse Trendelenberg position to facilitate visualization and access of the liver. Two 12-mm Versaport V2 single-use trocars (U.S. Surgical) were placed one to two centimeters cephalad to the midline port and one to two centimeters from the lateral boarder of the rectus sheath on the left and right sides of the abdomen.

After verification of the site and approach for the liver biopsy, a 45-mm GIA II Universal endoscopic stapler and roticulator de-

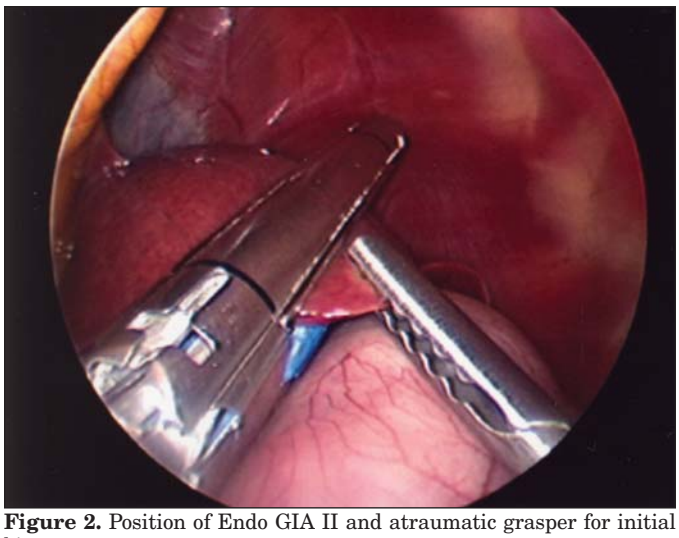

Figure 2. Position of Endo GIA II and atraumatic grasper for initial biopsy.

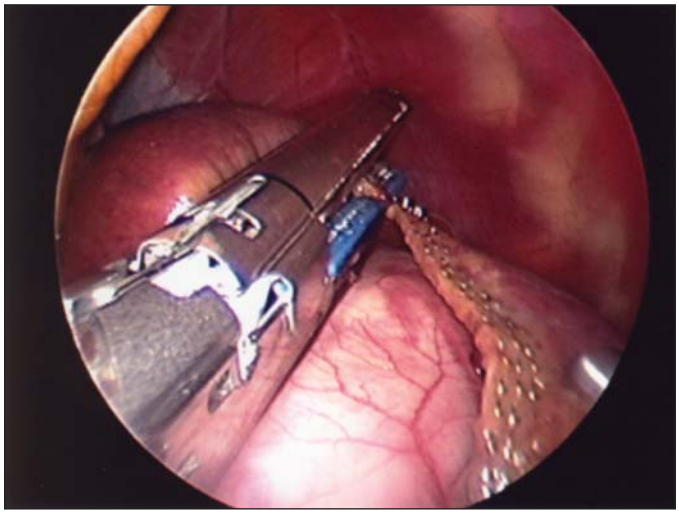

Figure 3. Stapling by use of an Endo GIA II to divide and provide hemostasis.

vice (U.S. Surgical) was introduced into the right 12-mm port. The left lateral lobe of the liver was maneuvered into the jaws of the Endo GIA Universal, using an atraumatic grasper through the left-side port (Fig. 2). The endoscopic stapling device places two, triple-staggered rows of titanium staples (6 rows total) while simultaneously dividing the tissue exactly in the middle of the third and fourth row (Fig. 3). The first biopsy specimen was then removed through the left-side port. A second biopsy specimen was taken from the same lobe or an adjacent lobe of the liver. A 60-mm Endo GIA stapler load was used to take this specimen. If the specimen was incompletely transected using the stapler, the remaining tissue was cut with laparoscopic scissors introduced from the monkey's right-side port.

Just prior to division of the specimen, an Endo Catch endoscopic retrieval bag (U.S. Surgical) was placed through the left-hand port and positioned to capture the specimen (Fig. 4). The Endo Catch bag as well as the port were removed entirely as quickly as possible after ensuring that the ring was retracted to avoid inadvertent injury to viscera and that the bag had closed over the specimen (Fig. 5). The specimen was removed via the left-hand port and immediately clamped in a vise grip chilled in liquid

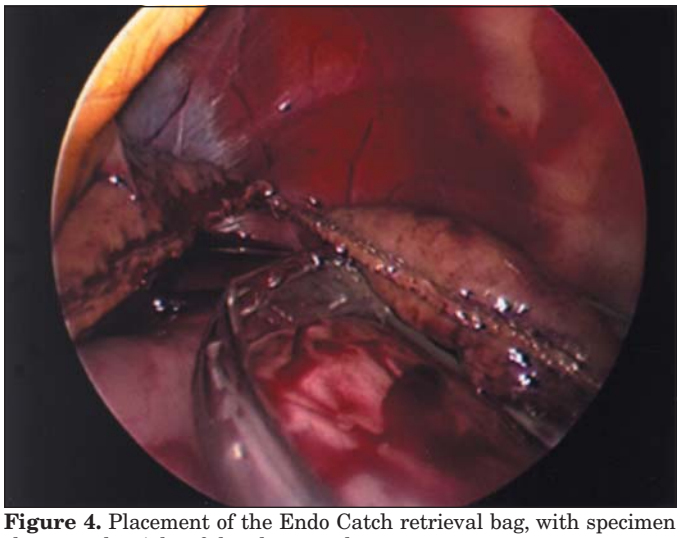

Figure 4. Placement of the Endo Catch retrieval bag, with specimen shown to the right of the photograph.

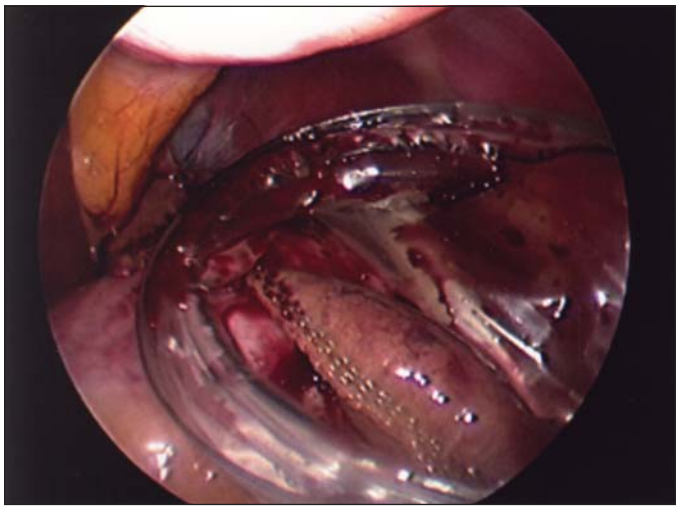

Figure 5. Transected liver specimen in retrieval bag.

nitrogen.

The cut edge of the liver generally had minimal bleeding, due to the hemostatic stapling provided by the Endo GIA. However, to ensure hemostasis, the endoscopic monopolar coagulator (25 W) was applied to the biopsy edge. Great care was taken to ensure that there was no inadvertent thermal injury to the surrounding organs and that adequate hemostasis of the liver edge was achieved (Fig. 6).

The omental AT biopsy specimens were obtained using the atraumatic grasper to lift a tongue of omentum through the right-hand port and bring the omentum out of the abdomen. The specimen was ligated with a 3-0 silk tie and divided by use of Metzenbaum scissors.

All port sites were closed with 0-vicryl sutures in interrupted pattern. The skin was closed in a subcuticular pattern, and Dermabond (Ethicon, Inc., Somerville, N.J.), a sterile, topical skin adhesive, was applied to the incisions. Buprenorphine (0.3 mg/kg) was given as a postoperative analgesic.

Results

Nine obese rhesus monkeys each underwent two minimally invasive laparoscopic procedures, approximately six weeks apart,

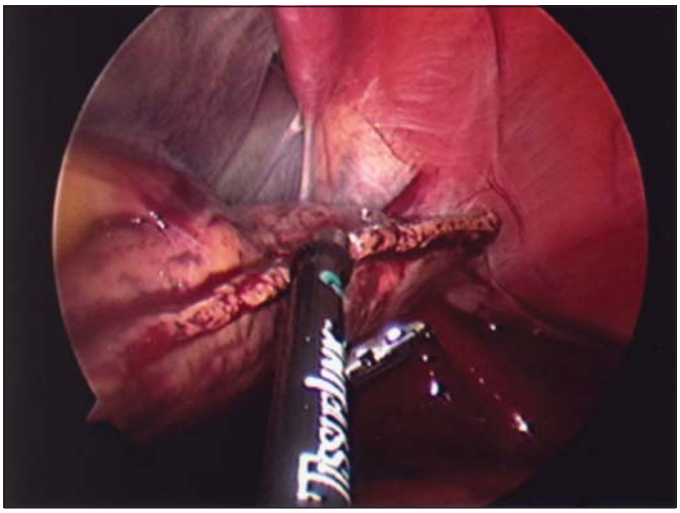

Figure 6. Staple line on the liver edge after transection, using the Endo GIA stapler and the TissueLink Floating Ball coagulator to ensure hemostasis.

for liver and omental AT sampling. All monkeys tolerated the procedures well, with full recovery after the initial and repeat laparoscopic procedures.

Duration of insufflation was 30 ± 3 (mean ± SEM; range, 11 to 57) min, with intra-abdominal pressure from 8 to 12 mmHg. The initial liver specimen, which was not time-sensitive according to protocol, weighed 2.1 ± 0.4 g, and was divided, removed from the peritoneal cavity, and fixed in 1.6 (94 ± 10; range, 62 to 136) seconds. The second liver specimen, which was time-sensitive, weighed 5.0 ± 0.5 g and was divided, removed from the peritoneal cavity, and freeze-clamped ex situ in less than a minute (45 ± 8 seconds; range, 16 to 110 seconds). The omental AT specimen weighed 16.6 ± 0.8 g.

There were no major complications following either initial or repeat laparoscopy. One monkey, early in the study, removed sutures from its midline abdominal incision. The sutures were replaced, and it recovered without further problems. One monkey had bruising around the port sites for one to two days during the postoperative period. In all monkeys, minimal adhesions were noted on repeat laparoscopy, at the liver biopsy site along the divided edge. These few adhesions were mild and nearly avascular, and could be easily snipped and or dissected free, using the endoscopic forceps. A single adhesion was noted at the midline port site of one monkey at the time of the second laparoscopy, and another monkey had a single adhesion on the lateral port.

Discussion

The laparoscopic technique has experienced remarkable growth in the last decade. Many complex surgical procedures, previously performed exclusively via an open surgical approach (laparotomy), are now routinely done through use of minimal-access techniques. Dr. Phillip Bozzini, the "Father of Endoscopy," developed the first known endoscope about 1804 that consisted of a wax candle within a leather-covered tin lantern, with which he illuminated the mouth, nose, ears, and other body cavities (19). In the 1860s, cystoscopy and hysteroscopy were successfully initiated, but difficulties with inadequate illumination and tube length impeded use of the technique for gastroscopy.

In 1902, the first abdominal endoscopic procedure was initiated by Kelling, who described inspection of the peritoneal cavity of a dog by use of a cystoscope (23). Interestingly, in 1910, Jacobaeus (21) developed a trocar with a valve to prevent loss of air and used a cystoscope and insufflation of the abdominal cavity with filtered air to further refine this approach. Jacobaeus was a prolific writer, and termed his procedure "laparoscopy," probably the most generally used term today for abdominal endoscopy (19). Another milestone in the use of laparoscopy was the development of flexible fiber optic glass bundles (generally attributed to the work of Semm [34]), through which high levels of illumination and, ultimately, transmission of a return image from the endoscope to a camera could be achieved (19).

For some time, limitations in cameras and instrumentation determined the types of procedures that could be performed. Specifically, the lens rod scope could only be used by direct visualization, using a complicated mirror system that was operated with the aid of an assistant. The development of a charged coupled device (CCD) camera was critical for development of more complicated and advanced procedures (5). In human medicine, laparoscopy was initially embraced by gynecologists. In 1991, Muhe introduced the surgical approach of laparoscopic cholecystectomy (24). The minimally invasive approach was a welcome innovation and, over time, increasingly advanced procedures were accomplished as techniques improved.

In the research setting, some of the initial applications of laparoscopy in animals were done for reproductive studies (6), and in animals as well as humans, laparoscopy has been used for diagnostic and therapeutic interventions. Dukelow and Ariga (12) used laparoscopy in a wide range of species, including rodents, rabbits, minks, chickens, dogs, cats, galagos, squirrel monkeys, macaques, baboons, goats, sheep, swine, and cattle. Specific animal research reports have included the use of laparoscopy to study reproductive function in the rhesus monkey (11) and chimpanzee (15). Laparoscopy has also been adapted for wide use in zoological medicine (birds, reptiles, foxes, bears, cheetahs, jaguars, tigers, lions, and gorillas [7]). For research purposes, it has been performed in baboons to obtain liver and splenic biopsy specimens (9, 32), in rhesus monkeys for performing serial kidney, spleen, small intestine, and lymph node biopsy for HIV studies (31), and in rhesus monkeys for the study of hepatectomy and liver regeneration (14). Furthermore, increasing use of laparoscopic procedures in the clinical area has driven the development of more advanced instrumentation.

Currently, endoscopes vary from two to 12 mm in diameter, are straight and angled, and include channels for passage of instruments for biopsy, hemostasis, and cauterization, or adjacent port sites allow direct instrumentation for these options. We applied our experience with liver wedge biopsy in humans to use specialized instrumentation, specifically the Endo GIA stapler device, to divide the liver specimen and provide a good measure of hemostasis in the retrieval of specimens. Additionally, we were able to use a recently developed saline-infused, radio-frequency tissue ablator to ensure hemostasis and avoid charring and other problems in delicate tissues with direct electrode contact.

Our study was unique in that our specimens were time sensitive. Specimen retrieval had to be completed as rapidly as possible and the specimen had to be quickly frozen to preserve enzyme activity. In addition, our subjects included older and obese monkeys, with potentially greater medical risks associated with these conditions. In humans as well as animals (9), high in-

tra-abdominal pressure was associated with adverse physiologic changes, including impaired diaphragmatic excursion, retention of CO_2, and reduced visceral perfusion. In the study reported here, we achieved a safe level of pneumoperitoneum (eight to 12 mmHg) that did not cause physiologic detriment and did not compromise visualization. There were no complications or deaths due to the procedure. In addition, the repeat procedures were smoothly and successfully carried out, without significant difference in the duration of insufflation when comparing the initial and repeat laparoscopy procedures (mean duration, 33 ± 5 versus 31 ± 4 min, respectively; $P = 0.3$).

We identified some limitations for the laparoscopic approach. Under optimal conditions with skilled personnel performing the procedure, liver specimens obtained via open biopsy can be divided and frozen within three to five seconds. Using the laparoscopic approach, we obtained a liver specimen of the appropriate size within 45 seconds, on average, but often within 16 to 20 seconds, which is rapid.

The ability to safely carry out a repeat procedure in this valuable primate model is clearly an advantage of the laparoscopic approach. As is well documented in humans, adhesion formation after laparoscopy in the primates was minimal or none, compared with adhesion formation after the open surgical procedures. The lack of adhesions greatly reduces the likelihood of complications, such as obstruction, which may arise from the open surgical approach to tissue sampling. In addition, using the laparoscopic, compared with the open surgical approach, we were able to obtain larger tissue specimens safely and efficiently and use of the Endo GIA stapler and the saline-infused coagulator greatly minimized bleeding and improved hemostasis of the liver edge.

In human patients, minimally invasive procedures have definite advantages over open surgical procedures, including rapid return to normal physical activity, reduction in postoperative pain, lower incidence of wound complications, such as hernia, and lower incidence of adhesion formation. Similar advantages have been reported in veterinary literature as well. Rawlings and coworkers (32) reported that their baboons had earlier return to normal activity and eating. As documented in our study, these primates, although older and obese, did extremely well when the laparoscopic approach was done. Earlier recovery, as evidenced by quicker return to normal physical activity and eating behavior, greatly decreased postoperative discomfort, and return to normal routine were observed in these subjects. Repeat operations were as straight forward as the initial tissue sampling due to lack of adhesion formation. Indeed, there were no adhesions at all in response to repeat laparoscopy in all but two monkeys, and in all subjects, the previous port sites were used without difficulty in the repeat laparoscopy.

In conclusion, 18 procedures in nine obese rhesus monkeys were successfully carried out, using minimally invasive surgery to obtain time-sensitive liver and omental AT specimens. Comparing the laparoscopic approach with conventional surgical laparotomy for liver wedge resection, the duration of surgery averaged about 30 min versus two hours, respectively. In addition, the monkeys experienced faster postoperative recovery via laparoscopy, rapid return to normal food intake and physical activity, and excellent wound healing without complications. We conclude that minimally invasive surgery by laparoscopy greatly decreases anesthesia and operative time, provides intra-abdominal tissue specimens in a time-efficient manner, decreases surgical complications, and facilitates rapid and full recovery of the primate.

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References

1. **Bodkin, N. L., J. S. Hannah, H. K. Ortmeyer, and B. C. Hansen.** 1993. Central obesity in rhesus monkeys: association with hyperinsulinemia, insulin resistance, and hypertriglyceridemia? Int. J. Obes. **17:**53-61.
2. **Bodkin, N. L. and B. C. Hansen.** 1995. Antihypertensive effects of captopril without adverse effects on glucose tolerance in hyperinsulinemic rhesus monkeys. J. Med. Primatol. **24:**1-6.
3. **Bodkin, N. L., B. L. Metzger, and B. C. Hansen.** 1989. Hepatic glucose production and insulin sensitivity preceding diabetes in monkeys. Am. J. Physiol. **256** (Endocrinol. Metab.)**:**E676-E681.
4. **Bodkin, N. L., H. K. Ortmeyer, and B. C. Hansen.** 1993. Diversity of insulin resistance in monkeys with normal glucose tolerance. Obes. Res. **1:**364-370.
5. **Bordelon, B. and J. Hunter.** 1994. Endoscopic technology, p. 6-18. *In* F. Greene and J. Ponsky (ed.), Endoscopic surgery. W. B. Saunders Co., Philadelphia.
6. **Bosu, W.** 1973. Laparoscopic technique for the examination of the ovaries in the rhesus monkey. J. Med. Primatol. **2:**124-129.
7. **Bush, M., D. E. Wildt, S. Kennedy, and S. W. Seager.** 1978. Laparoscopy in zoological medicine. J. Am. Vet. Med. Assoc. **173:**1081-1087.
8. **Cornblath, D. R., M. A. Hillman, J. S. Striffler, C. N. Herman, and B. C. Hansen.** 1989. Peripheral neuropathy in diabetic monkeys. Diabetes **38:**1365-1370.
9. **D'Hooghe, T. M., C. S. Bambra, I. O. Farah, B. M. Raeymaekers, and P. R. Koninckx.** 1993. High intraabdominal pressure: effects on clinical parameters and lung pathology in baboons (*Papio cynocephalus* and *Papio anubis*). Am. J. Obstet. Gynecol. **169:**1352-1356.
10. **deKoning, E. J. P., N. L. Bodkin, B. C. Hansen, and A. Clark.** 1993. Diabetes mellitus in *Macaca mulatta* monkeys is characterized by islet amyloidosis and reduction in beta-cell population. Diabetologia **36:**378-384.
11. **Dierschke, D. J. and J. R. Clark.** 1976. Laparoscopy in *Macaca mulatta*: specialized equipment employed and initial observations. J. Med. Primatol. **5:**100-110.
12. **Dukelow, W. R. and S. Ariga.** 1976. Laparoscopic techniques for biomedical research. J. Med. Primatol. **5:**82-99.
13. **Erwin, J. and E. Zucker.** 1987. African monkeys in behavioral research: a 5 year retrospective analysis, p. 1-21. *In* E. Zucker (ed.), Comparative behavior of African monkeys. Alan R. Liss, New York.
14. **Gaglio, P. J., G. Baskin, R. Bohm, Jr., J. Blanchard, S. Cheng, B. Dunne, J. Davidson, H. Liu, and S. Dash.** 2000. Partial hepatectomy and laparoscopic-guided liver biopsy in rhesus macaques (*Macaca mulatta*): novel approach for study of liver regeneration. Comp. Med. **50:**363-368.

15. **Graham, C. E.** 1976. Technique of laparoscopy in the chimpanzee. J. Med. Primatol. **5:**111-123.
16. **Hannah, J. S., R. B. Verdery, N. L. Bodkin, B. C. Hansen, N.-A. Le, and B. V. Howard.** 1991. Changes in lipoprotein concentrations during the development of noninsulin dependent diabetes mellitus in obese rhesus monkeys (*Macaca mulatta*). J. Clin. Endocrinol. Metab. **72:**1067-1072.
17. **Hansen, B. C. and N. L. Bodkin.** 1985. Beta cell hyperresponsiveness to glucose precedes both fasting hyperinsulinemia and reduced glucose tolerance. (Abstr.) Diabetes. **34 (Suppl. 1):**8A.
18. **Hansen, B. C. and N. L. Bodkin.** 1986. Heterogeneity of insulin responses: phases in the continuum leading to non-insulin-dependent diabetes mellitus. Diabetologia **29:**713-719.
19. **Harrison, R. M.** 1976. The development of modern endoscopy. J. Med. Primatol. **5:**73-81.
20. **Hill, B.** 1977. The rhesus monkey (*Macaca mulatta*): history, management and scientific investigation. The Charles River Breeding Laboratories. **16:**1-7.
21. **Jacobaeus, H. C.** 1910. Uber die Moglichkeit die Zystoskopie bei Untersuchung seroser Hohlungen anzuwenden. Munch. med Wschr. **57:**2090-2092.
22. **Jen, K.-L. C., B. C. Hansen, and B. L. Metzger.** 1985. Adiposity, anthropometric measures, and plasma insulin levels of rhesus monkeys. Int. J. Obes. **9:**213-224.
23. **Kelling, G.** 1902. Uber Oesophagoskopie, Gastroskopie und Kolioskopie. Munch. med. Wschr. **49:**21.
24. **Muhe, E.** 1991. E Laparoskopische Cholezystecktomie-Spatergebnesse. Langenbecks Arch. Chir. Suppl. 416-423.
25. **National Research Council Commission on Life Sciences—Institute of Laboratory Animal Resources.** 1996. Guide for the care and use of laboratory animals. National Academy Press, Washington, D.C.
26. **Oliver, W. R., Jr., J. L. Shenk, M. R. Snaith, C. S. Russell, K. D. Plunket, N. L. Bodkin, M. C. Lewis, D. A. Winegar, M. L. Sznaidman, M. H. Lambert, H. E. Xu, D. D. Sternbach, S. A. Kliewer, B. C. Hansen, and T. M. Willson.** 2001. A selective peroxisome proliferator-activated receptor delta agonist promotes reverse cholesterol transport. Proc. Natl. Acad. Sci. USA **98:**5306-5311.
27. **Ortmeyer, H. and N. Bodkin.** 1998. Lack of defect in insulin action on hepatic glycogen synthase and phosphorylase in insulin-resistant monkeys. Am. J. Physiol. (Gastrointest. Liver) **274:**G1005-G1010.
28. **Ortmeyer, H. K., N. L. Bodkin, and B. C. Hansen.** 1993. Adipose tissue glycogen synthase activation by in vivo insulin in spontaneously insulin-resistant and Type 2 (non-insulin-dependent) diabetic rhesus monkeys. Diabetologia **36:**200-206.
29. **Ortmeyer, H. K., N. L. Bodkin, and B. C. Hansen.** 1993. Insulin-mediated glycogen synthase activity in muscle of spontaneously insulin-resistant and diabetic rhesus monkeys. Am. J. Physiol. **265** (Regulatory Integrative Comp. Physiol. 34)**:**R552-R558.
30. **Ortmeyer, H. K., N. L. Bodkin, and B. C. Hansen.** 1997. Insulin regulates liver glycogen synthase and glycogen phosphorylase activity reciprocally in rhesus monkeys. Am. J. Physiol. (Endocrinol. Metab.) **272:**E133-E138.
31. **Perret-Gentil, M. I., M. N. Sinanan, M. B. Dennis, D. M. Anderson, H. B. Pasieka, J. T. Weyhrich, and T. A. Birkebak.** 2000. Videoendoscopic techniques for collection of multiple, serial intra-abdominal biopsy specimens in HIV-negative and HIV-positive pigtail macaques (*Macaca nemestrina*). J. Invest. Surg. **13:**181-195.
32. **Rawlings, C. A., S. Van Lue, C. King, L. Freeman, R. T. Damian, C. Greenacre, A. Chernosky, F. M. Mohamed, and T. M. Chou.** 2000. Serial laparoscopic biopsies of liver and spleen from *Schistosoma*-infected baboons (*Papio* spp.). Comp. Med. **50:**551-555.
33. **Robison, W. and N. Laver.** 1991. Diabetic retinal microangiopathies in humans and animals models: similar histological progressions. Invest. Ohthalmol. Visual Sci. **32:**915.
34. **Semm, K.** 1969. Gynaecological pelviscopy and its instrumentarium. Acta Eur. Fertil. **1:**81-97.
35. **Spoerri, P. E., W. G. Robison, D. Player, A. B. Groome, T. Alexander, N. L. Bodkin, B. C. Hansen, and M. B. Grant.** 1998. Diabetes related increase in plasminogen activator inhibitor-1 expression in monkey retinal capillaries. Int. J. Diabetes **6:**15-27.
36. **Winegar, D. A., P. J. Brown, W. O. Wilkison, M. C. Lewis, R. J. Ott, W. Q. Tong, H. R. Brown, J. M. Lehmann, S. A. Kliewer, K. D. Plunket, J. M. Way, N. L. Bodkin, and B. C. Hansen.** 2001. Effects of fenofibrate on lipid parameters in obese rhesus monkeys. J. Lipid Res. **42:**1543-1551.