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*Original Research*

# Chronic Collection of Cerebrospinal Fluid from Rhesus Macaques (*Macaca mulatta*) with Cisterna Magna Ports: Update on Refinements

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**More than 20 y ago, we developed an animal model for chronic and continuous collection of cerebrospinal fluid (CSF) from conscious rhesus macaques. Since our previous publication in 2003, we have successfully implanted 168 rhesus macaques using this approach. Our experience enables us to provide up-to-date information regarding the model, including refinements to our implant design, reductions in maintenance, and new procedures for dealing with contamination. The results of our experiences have reduced the number of surgeries required and helped to increase the longevity of the implant, with some functioning for more than 18 y. Building on our success in rhesus macaques, we attempted to develop similar animal models in the African green monkeys and dogs but have been unable to develop reliable chronic models for CSF collection in these species.**

**Abbreviation:** CMP, cisterna magna port; CSF, cerebrospinal fluid

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Cerebrospinal (CSF) biomarkers and pharmacokinetics are reliable tools for monitoring the therapeutic effect of compounds used for the treatment of various neurodegenerative diseases. CSF can be collected by using several methods, including lumbar and cisterna magna punctures or implanted devices.[3,6,8,9,11-13] Each method has its own specific challenges but no matter which technique is used, performing CSF collections safely is imperative to avoiding risks to the animals and to providing the best CSF samples for analysis.[1] To support our research focus on neurocognitive disorders (including Alzheimer disease, Parkinson disease, and sleep disorders), we developed an NHP model of chronic CSF collection (the cisterna magna port [CMP] model) more than 20 y ago.[4] This model allows safe, repeatable and reliable collections of CSF samples from the cisterna magna in conscious rhesus macaques (*Macaca mulatta*). The information summarized herein updates this animal model since its introduction in 2003 and reflects our 18 additional years of experience with it. We also provide information regarding our attempts to develop CMP models in African green monkeys and dogs. We recommend that readers review the 2003 article for further information and understanding of the CMP model.[4]

## Materials and Methods

**Animals.** All animals were housed at our facility (Merck and Company, Kenilworth, NJ). All procedures were performed in accordance with established guidelines and were reviewed and approved by the IACUC. Animals were pair-housed when possible and cared for in an AAALAC-accredited facility and animal care program. Housing requirements for each species were in accordance with The Guide.[5]

**Rhesus macaques (*Macaca mulatta*).** Since our previous publication in 2003, 219 rhesus macaques (175 males, 44 females) underwent surgery for the implantation of a CMP for chronic CSF collection.[4] These macaques were of Indian origin, captive-bred, and obtained from an SPF, closed colony in the United States. Primary housing was based on animal height and weight and would have been either 4.3 or 6.0 quads. Room temperature range was 65-73°F with a target midpoint of 69°F and relative humidity range was 30-70% with a target midpoint of 50%. Before surgery, all animals were acclimated to conscious restraint. Macaques were fed a commercially prepared primate diet (High Protein Monkey Diet 5045, PMI Nutrition International, St Louis, MO). Water was available ad libitum. Environmental enrichment included a hanging mirror permanently placed on all cages as well as rotation of inner (10 different items) and outer (4 different items) cage manipulanda which was changed every two weeks. Foraging material and rotation of daily fruit and vegetables were provided as well. Approved television and music were also given at a minimum of once per week.

**African green monkeys (*Chlorocebus aethiops*).** Between 2007 and 2020, 22 African green monkeys (14 male, 8 female) underwent surgery for the implantation of a CMP for chronic CSF collection. These monkeys were captive bred in a closed colony in the United States. Primary housing was a Summit cage which is 6.0 sq ft inside space and 32″ tall. Room temperature range was 65-75°F with a target midpoint of 72°F and relative humidity range was 30-70% with a target midpoint of 50%. Before surgery, all animals were acclimated to conscious restraint. Animals were fed a commercially prepared primate diet (High Protein Monkey Diet 5045; PMI Nutrition International). Water was available ad libitum. Environmental enrichment included

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a hanging mirror permanently placed on all cages as well as rotation of inner (10 different items) and outer (4 different items) cage manipulanda which was changed every two weeks. Foraging material and rotation of daily fruit and vegetables were provided as well. Approved television and music were also given at a minimum of once per week.

**Dogs (*Canis familiaris*).** Between 2005 and 2011, 95 purpose-bred dogs (beagles; 76 male, 19 female) underwent surgery for the implantation of a CMP for chronic CSF collection. Primary housing consists of permanent pens. Room temperature range was 64-77°F with a target midpoint of 69°F and relative humidity range was 30-70% with a target midpoint of 50%. Animals were fed dry dog food (Laboratory Canine Diet 5006, PMI Nutrition International). Water was available ad libitum. Environment enrichment included social housing between two pens when possible and rotation of inner cage toys.

**Implantation.** The catheter used for implantation is a novel design that we developed internally; it has undergone a few minor modifications since our 2003 publication.[4] Our current CMP catheters (CMC-06) are produced by SAI Infusion Technologies (Lake Villa, IL) and are attached to a titanium port body (SoloPort MIN-C50, Access Technologies, Skokie, IL) during the surgical placement of the implant. The original 3.5-Fr silicone catheter was successful, but we since transitioned to a larger (5-Fr) catheter because it provides a better CSF flow rate and is more durable over time with fewer breaks. The catheter tip entering the cisterna magna was 1.0 cm long in the original catheter design. However, a 2007 MR image of an implanted rhesus macaque (Figure 1) demonstrated physical depression of the brain stem, suggesting that 1.0 cm might be too long in smaller animals. Although the affected animal had no clinical issues, we subsequently refined the catheter tip so that only 5 mm of catheter enters the cisterna magna.

The original implant design used 2 silicone collars to allow appropriate positioning and securing of the implant. The fixed collar that is placed in the cisterna magna has not been changed, but the collar that would be external to the atlantooccipital membrane was changed to a fixed disc. In 2005, we determined that the external collar did not always hold the catheter in place and sometimes allowed too much catheter to enter the cisterna magna, thereby causing model failure (no CSF flow) and potential neurologic complications (e.g., head tilt, nystagmus, ataxia). The current design (Figure 2) includes a 1-cm silicone disc that is fixed in place during implant production. The fixed disc and fixed collar are separated by approximately 0.5-mm gap in which the atlantooccipital membrane sits after completion of surgical implantation. Tissue glue is no longer needed during surgery, as all components of the catheter are now fixed. The surgical implantation procedures remain unchanged and have proven to be successful over time.[4]

The anesthetic and antibiotic protocols remain unchanged, but we have instituted multimodal analgesia to optimize pain management. Our current preoperative analgesia plan still involves buprenorphine (0.01 mg/kg IM) but now also includes the administration of the NSAID carprofen (4.4 mg/kg SC) and a local anesthetic (bupivacaine, 2.0 mg/kg SC) at each skin incision. On the morning after surgery, animals receive a second dose of carprofen. Macaques are evaluated daily for appropriate healing and pain control, and additional doses of analgesics are given as needed for at least 10 d postoperatively. Macaques recover for a minimum of 14 d before their collars are replaced and they are scheduled for studies. During this recovery phase, CMP maintenance is performed in anesthetized animals to maximize the success of the model.

**Maintenance.** Maintenance procedures remain as described previously, but their frequency has been reduced dramatically.[4] Initially for successfully implanted animals received routine maintenance procedures 3 times per week; this schedule was reduced to twice weekly at the time of the 2003 publication.[4] In 2009, we began once-weekly maintenance procedures, and in 2012, we began a maintenance regimen in which all animals whose CMP had remained patent for at least 4 mo after surgical implantation received maintenance every 3 wks. Because all implants remained patent with maintenance every 3 wk, we changed the frequency to every 4 wk; this regimen has been successful thus far. We recommend that animals in which the CSF flow rate is lower than 0.5 mL/min should be returned to twice-weekly flushing until either the flow rates improve or a surgical repair is required. This reduction in CMP maintenance had not been associated with any significant increase in implant failure due to loss of patency. However, we have noted a reduction in the number of repair surgeries needed to replace access ports because the injection area was wearing out due to the high number of needle punctures. With the original maintenance procedures, access ports were replaced every 21 mo on average (range, 14 to 30 mo). When maintenance procedures were reduced to once per week, port replacement was necessary every 27 mo on average (range, 16 to 34 mo). With our current maintenance procedures, access port exchange surgeries are necessary much less frequently, at approximately every 48 mo (range, 22 to 107 mo). Another added benefit of a reduced maintenance schedule is that less port access is required, thereby reducing the risk of contaminating the implant.

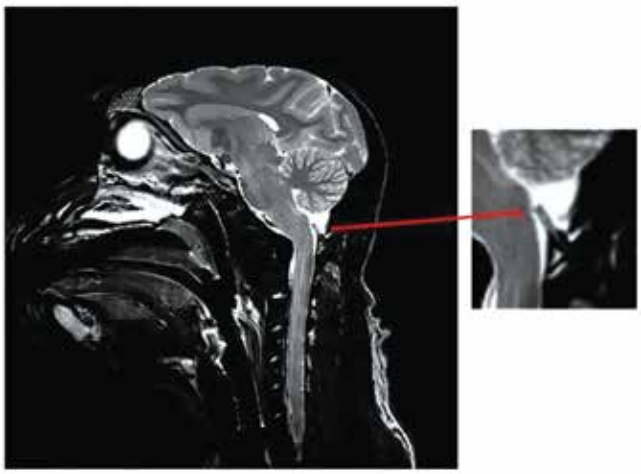

**Figure 1.** MR image showing a slight depression on the brain stem due to the physical presence of the 1.0-cm silicone catheter tip.

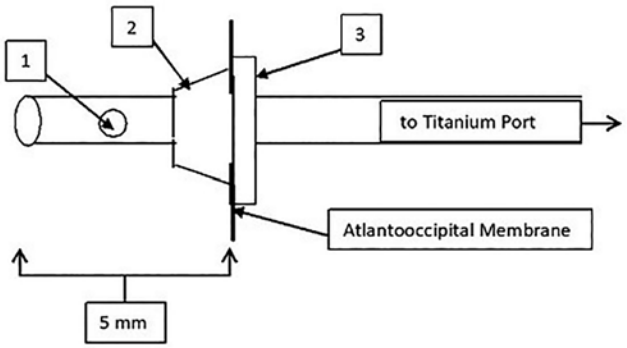


**Figure 2.** Schematic diagram of the current cisterna magna port implant (5.0-Fr silicone catheter). 1, side hole; 2, fixed, tapered silicone collar; 3, fixed silicone disc.

**Culturing of CSF and treatment of contaminated models.** During routine maintenance procedures, CSF samples are cultured every other month to monitor for contamination.[4] When bacterial growth was confirmed with 2 positive cultures (second culture includes cytology), our older procedures involved CMP removal and systemic antibiotic treatment. However, in 2010, we began treating contaminated CMP with antibiotic treatment administered both within the CMP and systemically. The intraCMP treatment procedure begins as routine maintenance of the implant in a conscious chaired monkey. Prior to the final flush of sterile saline through the implant, a small volume (0.3 mL) of antibiotic is flushed into the port and catheter. We can attest only to the successful use of the antibiotic enrofloxacin (Baytril) in animals for which CSF culture results demonstrate enrofloxacin sensitivity. Extreme caution is necessary if other antibiotics are used for intraCMP treatment, because we have noted severe adverse reactions to cephalosporins and aminoglycosides. The small volume of antibiotic injected into the CMP remains in the catheter briefly (approximately 5 min), followed by the usual volume of flush of sterile saline. The chaired macaque is monitored for 5 to 10 min after the final flush to observe for complications (most commonly vomiting); when noted, a veterinarian is contacted for further assessment and treatment as deemed necessary. If an animal demonstrates complications with the antibiotic injection, with future treatments the volume of antibiotic is withdrawn from the system after the 5-mins and prior to the final sterile saline flush. In most cases, we have seen successful clearance of CMP contamination after 2 wk of twice-weekly intraCMP antibiotic injection. We recommend that if a *Bacillus* species is cultured, treatment should be extended to 3 wk. During this period, systemic antibiotic treatment that is based on culture and sensitivity results and on the ability of the antibiotic to pass the blood–brain barrier can be initiated.[10] Most commonly, we have used ampicillin or ceftriaxone (Rocephin) and occasionally gentamicin for systemic treatment once daily for 10 d. Two weeks after all antibiotic treatments have been completed, the CSF is recultured to ensure that the contamination has cleared; if so, the animal is released for study usage. When infection remains, another round of treatment can occur, or the CMP can be removed surgically and the animal retreated systemically.

## Results

Since the 2003 publication, we have revised our definition of success regarding the chronic rhesus CMP model,[4] because our experience has raised our expectations of model performance. We originally defined model success as consistent patency for CSF collection for longer than 2 wk postoperatively and the completion of a single study. Currently, we consider a rhesus CMP model to be successful once it reaches the fourth month of patency and is placed on maintenance procedures of once every 4 wk. Many animals are used successfully prior to that point but these have not been the truly reliable, chronic CMPs that we expect.

Between 2004 and 2020, 219 rhesus monkeys (175 male, 44 female) have undergone surgery to establish our CMP colony. Of these 219 surgeries, 168 (136 male and 32 female macaques) have been successful; this success rate (77%) is higher than that in the original publication (58% success rate).[4] At any given time, our functional CMP colony consists of approximately 30 animals. The duration of patency for successful CMPs varies from several months to several years. Our oldest successful implanted animal provided consistent CSF collection for just over 18 y and was lost due to euthanasia from other age-related health issues. The flow rate in our colony of successful models varies between animals and even within an individual animal from day to day. The expected (and observed) flow rate in a successful model from our colony ranges from 0.5 to 2.0 mL/min.

**Contamination of ports.** Despite adhering to aseptic techniques when maintaining and using this CMP model, we still experience occasional contamination. These contaminations are likely due to use of the port in conscious macaques, which carries the potential for contamination from aerosolization of debris and dander due to movement of the animals and personnel during the access procedures. In addition to aseptic technique, to further mitigate the risk of contamination, we restrain the macaques during port access. Furthermore, we access the ports in a clean environment in a low-traffic area, involve the fewest personnel required to perform the task, and ensure that personnel don the appropriate personal protective equipment.

Between 2003 and 2020, our rhesus CMP colony had 117 confirmed contaminations (53% infection rate). Prior to instituting our intraCMP antibiotic treatment in 2010, we had confirmed 66 CMP infections (50% of our colony) at some point; all of these macaques required implant removal and systemic antibiotic treatment. After 2010, when we instituted intraCMP antibiotic treatment, we confirmed contamination in 51 CMP animals (23% of our colony) but successfully cleared the contamination in 41 (80%), thus averting removal of these animals from our CMP colony; intraCMP treatment failed to clear the contamination in the remaining 10 animals (20%), which were ultimately removed from the colony to allow treatment. The common contaminants that we detected and successfully treated are *Staphylococcus* spp. (51% of cases; *S. auricularis*, *S. warneri*, *S. hominis*, *S. epidermidis*) and *Bacillus* spp. (49%; *B. cereus*, *B. mycoides*, *B. circulans*, *Alicyclobacillus acidoterristris*, *Paenibacillus polymyxa*, *Brevibacillus choshienensis*). All 26 cases of contamination by a *Staphylococcus* species were completely cleared through intraCMP treatment. In contrast, macaques contaminated with a *Bacillus* species (25 cases) were cleared only 64% of the time even with the extra week of treatment. Clearing contamination in these animals by using the intraCMP antibiotic technique has greatly reduced the number of surgeries that would have been required and has prevented the loss of animals from the colony, allowing them to remain available for research needs. In addition, our intraCMP treatment has reduced the number of macaques necessary to replace animals that would have otherwise been lost due to contamination, thereby adhering to the 3 Rs.[5]

**CSF analysis after the treatment of and recovery from contamination.** We previously reported a clinical chemistry analysis of CSF collected from our CMPs.[4] Here we report the results of analysis of CSF collected from 5 CMPs that never demonstrated contamination as compared with 4 samples from CMPs that had been contaminated but were cleared after using the intraCMP antibiotic treatment protocol. During a routine maintenance procedure, CSF samples were taken from both groups of animals and submitted to our internal diagnostic lab, where the samples were spun at 500 × *g* for 5 min at 22 °C to clear any potential cellular debris. The supernatant was then analyzed on an Atellica CH930 chemistry instrument (Siemens, Erlangen, Germany). The tests used included linear rate reaction (ALP, AST, ALT, creatine kinase, BUN), end point (total protein, creatinine, Ca, glucose), and integrated multisensor (Na, K, Cl) technology. The results of these analyses (Table 1) did not differ significantly between the 2 groups; therefore, we presume that animals cleared of contamination are still useful and can continue to provide valid data.

**Model translation to African green monkeys.** After the success of the CMP in rhesus macaques, we attempted to develop

**Table 1.** Analysis of CSF from never-contaminated rhesus CMP models compared with cleared contaminated models

| | Never contaminated ($n$ = 5) | | Cleared contaminated ($n$ = 4) | |
|---|---|---|---|---|
| | Range | Mean | | Mean |
| ALP (U/L) | <2 | — | <2 | — |
| ALT (U/L) | <5 | — | <5 | — |
| AST (U/L) | 12.4–18.0 | 15.2 | 15.3–16.6 | 15.9 |
| Total protein (mg/dL) | 15.1–22.8 | 18.9 | 12.2–29.9 | 20.7 |
| BUN (mg/dL) | 16.3–20.3 | 18.0 | 12.1–21.2 | 16.7 |
| Creatinine (mg/dL) | 0.3–0.4 | 0.3 | 0.3–0.4 | 0.33 |
| $Ca^{2+}$ (mg/dL) | 4.9–5.1 | 5.0 | 4.3–4.9 | 4.7 |
| Creatine kinase (U/L) | <11 | — | <11 | — |
| $Na^{+}$ (mmol/L) | 155–158 | 156 | 155–158 | 156 |
| $K^{+}$ (mmol/L) | 2.8–3.0 | 2.9 | 2.7–2.9 | 2.8 |
| Glucose (mg/dL) | 44–53 | 47 | 38–51 | 44 |

a CMP model in African green monkeys. Aged African green monkeys may offer a valuable animal model of Aβ deposition, gliosis, and neuritic dystrophy seen in brains of humans with Alzheimer disease.[2,7] Between 2007 and 2020, 22 (14 male, 8 female) African green monkeys underwent surgery to implant a CMP. Of the 20 animals successfully implanted (91%), only 8 (40%) resulted in a successful and functional model (that is, providing consistent patency for CSF collection for longer than 2 mo postoperatively at a flow rate greater than 0.5 mL/min). In the 8 successful implants (6 male, 2 female), the duration of patency ranged from 4 to 91 mo (average, 19 mo). The other 12 African green monkeys (60%) did not yield CSF with consistent reliability and were deemed to be unsuccessful models. Two 26-y-old female AG monkeys were not successful due to friability of the atlantooccipital membrane. We suspect that this friability is associated with age-related thinning of the membrane and recommend that care be taken when working with the thin, delicate atlantooccipital membrane that appears to be associated with aging.

The initial implant design used for African green monkeys was a 1-cm tip inserted into the cisterna magna, but we subsequently switched to a 5-mm tip, as we did with the rhesus CMP. In 2019, we took MR images of an African green monkey (Figure 3), which revealed that the cisterna magna of this species is not the same size as in rhesus monkeys. Consequently, we reduced the size of the catheter tips inserted into the cisterna magna to 3 mm. These refinements are showing promise in regard to animal model success and longevity; we therefore continue to evaluate CMP placement in African green monkeys as a potential subacute model.

**Model translation to dogs.** After the success of the CMP in rhesus macaques, we attempted to develop a canine CMP model. The transition of this methodology to dogs did not go as smoothly as anticipated. Between 2005 and 2011, 95 (76 male, 19 female) purpose-bred beagles underwent surgery to implant a CMP. In 12 dogs (13%), the port was never placed due to precluding anatomic variations or to rupture of a vertebral venous sinus, leading to bleeding that prevented adequate visualization of the atlantooccipital membrane. Of the 83 dogs (87%) that were successfully implanted, only 7 (8%) became successful and functional models (i.e., providing consistent patency for CSF collection for more than 2 mo postoperatively at a flow rate exceeding 0.5 mL/min). In the other 76 dogs (92%), CSF flow was unreliable, and we considered the implants to be unsuccessful. Most of these failures were related to fibrous growth

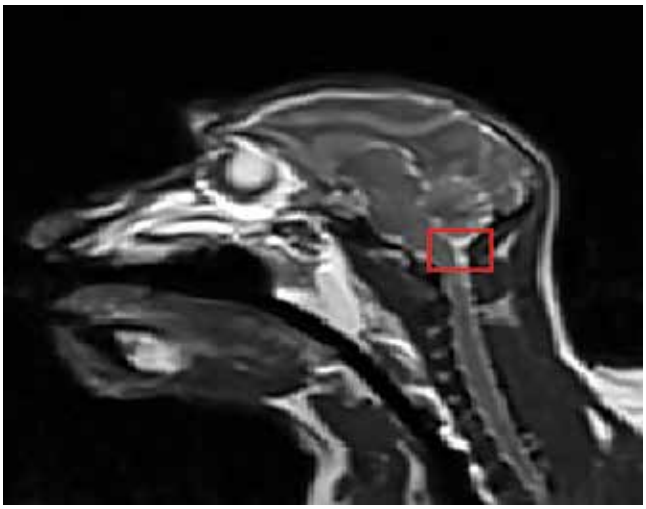

**Figure 3.** MR image of an African green monkey, demonstrating its smaller cisterna magna (noted within red box) as compared with that of a rhesus macaque.

over the catheter tip in the cisterna magna, which prevented CSF flow through the implant. Of the 7 successful models (all in males), the duration of patency ranged from 3 to 58 mo (average, 19 mo). Despite successful establishment and longevity of several attempts, the return on the investments was not ideal, and pursuit of a canine CMP model was abandoned in 2011.

## Discussion

The surgical approach and refined CMP design presented optimize the reliable and safe method that we previously established for chronic CSF collection in rhesus macaques, and this approach remains a proven alternative to more invasive and complicated procedures, such as intraventricular cannulations or laminectomy procedures.[3,9,11-13] In addition, despite reported improvement of techniques for routine cisterna magna taps,[6] our rhesus CMP model remains an ideal alternative with the advantages of little to no blood contamination, a low risk of temporary hypertension, and little risk of brainstem injury. Another advantage of the CMP system is that it provides a chronic, minimally invasive approach to collecting repeated CSF samples from conscious rhesus macaques. As we presented here, our new maintenance program has enabled us to perform fewer surgical procedures and to keep the animals healthy and with a low incidence of bacterial contamination. Our updated technique of intraCMP antibiotic treatment has allowed us to retain many animals after contamination. Overall, we have achieved a 77% success rate, with CMPs that potentially remain patent and useful for more than 18 y. As compared with a minimally invasive lumbar port model, our CMP model has similar success rates but far superior longevity.[8] Our model has become a vital tool in advancing our neuroscience programs from NHP to translational human clinical predictions and is in line with the guidance and recommendations of the Association of Primate Veterinarians.[1]

Our attempts to create an African green monkey CMP model have been less successful than the rhesus model, but we believe that the CMP model has potential for acute or subacute collection of CSF in African green monkeys. The main reason for using an acute or subacute model would be to collect CSF samples from a conscious animal without any potential interference from anesthetic drugs. The CSF samples would generally also be "cleaner" without potential blood contamination. However,

the CMP methodology is not ideal for chronic CSF collection in dogs and we suggest that researchers pursue alternative techniques for dogs.[3,8,11,12]

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