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Ancillary Procedures Necessary for Translational Research in Experimental Craniomaxillofacial Surgery

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Introduction: Swine are often regarded as having analogous facial skeletons to humans and therefore serve as an ideal animal model for translational investigation. However, there is a dearth of literature describing the pertinent ancillary procedures required for craniomaxillofacial research. With this in mind, our objective was to evaluate all necessary procedures required for perioperative management and animal safety related to experimental craniomaxillofacial surgical procedures such as orthotopic, maxillofacial transplantation.

Methods: Miniature swine (n = 9) were used to investigate perioperative airway management, methods for providing nutrition, and long-dwelling intravenous access. Flap perfusion using near-infrared laser angiography and facial nerve assessment with electromyoneurography were explored.

Results: Bivona tracheostomy was deemed appropriate versus Shiley because soft, wire-reinforced tubing reduced the incidence of tracheal necrosis. Percutaneous endoscopic gastrostomy tube, as opposed to esophagostomy, provided a reliable route for postoperative feeding. Femoral venous access with dorsal tunneling proved to be an ideal option being far from pertinent neck vessels. Laser angiography was beneficial for real-time evaluation of graft perfusion. Facial electromyoneurography techniques for tracing capture were found most optimal using percutaneous leads near the oral commissure.

Experience shows that ancillary procedures are critical, and malpositioning of devices may lead to irreversible sequelae with premature animal death.

Conclusions: Face-jaw-teeth transplantation in swine is a complicated procedure that demands special attention to airway, feeding, and intravascular access. It is critical that each ancillary procedure be performed by a dedicated team familiar with relevant anatomy and protocol. Emphasis should be placed on secure skin-level fixation for all tube/lines to minimize risk for dislodgement. A reliable veterinarian team is invaluable and critical for long-term success.

Key Words: Swine study, face transplant, translational study, craniofacial, craniomaxillofacial, ancillary procedure, PEG tube, Hickman catheter, tracheostomy, laser angiography, facial electromyography, maxillofacial transplant

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Craniomaxillofacial surgeons and researchers alike are constantly seeking new innovations for improved outcomes in both pediatric and adult patients.[1–3] As such, large animal studies often serve as the ideal vehicle for scientists and engineers testing novel concepts and techniques.[4,5] Unfortunately, translational research in large animals has been tempered by unfamiliar facial skeletal anatomy coupled with the vital functions affected by orthotopic facial transplant research including breathing, drinking, and feeding.[6]

Similar studies by Nobel laureate Joseph Murray et al[7] relied on a dog model for preliminary kidney transplant investigation, whereas Starzl et al used the nonhuman primate model for early liver transplant studies.[8] In parallel, our goal was to investigate the use of ancillary procedures required for experimental craniomaxiollofacial surgery such as face-jaw-teeth transplantation. This was a significant challenge given the absence of relevant literature available and thus the impetus for this study. Within this manuscript, we describe the main challenges encountered and propose remedies for the establishment of a preclinical swine model.

MATERIALS AND METHODS

This study was initiated in September 2011 after approval from our institution's Animal Care and Use Committee and has been conducted in strict accordance with the National Institutes of Health guidelines for the care and use of laboratory animals. Male and female Yucatan miniature swine (n = 9) weighing between 10 and 20 kg were used. All animals were sedated using 15 mg/kg of ketamine (100-mg/mL concentration; Lake Forest, IL) and 1 mg/kg of xylazine (Anased,

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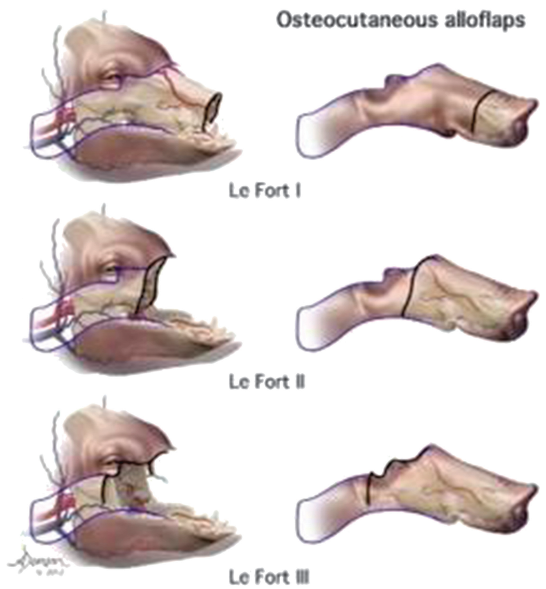
Fig 1 4/C



AQ2 **FIGURE 1.** Illustration depicting various levels of Le Fort-based, maxillofacial transplantation in swine as similar to humans.

Shenandoah, IA) intramuscularly and maintained with a mixture of isoflurane and oxygen (2–3 L/min). Continuous heart rate, blood pressure, and respiratory functioning were monitored throughout all phases of anesthesia and recovery.

A multidisciplinary craniofacial team within our university was established with collaboration from Research Animal Resources, which included veterinarians and technicians. Preliminary swine cadaver studies were led by the study's principal investigator (C.G.) and revealed relevant anatomic discrepancies in comparison with humans. Regular discussions followed before the first live surgery. Original planning included the use of a human Shiley tracheostomy device for airway management,[9] an esophagostomy tube for feeding based on previous investigations in feline,[10] and a tunneled intravenous external jugular vein catheter.[11] Intraoperative near-infrared laser angiography was needed for assistance with alloflap design and concern over facial vascularity.[12] Varying pedicle designs and bone cuts for Le Fort-based maxillofacial transplantation were assessed because of the novelty of the procedure (Fig. 1). With a secondary goal being to assess long-term facial motor recovery posttransplant,[13] facial electromyography was trialed on a limited basis using elementary half-face skin dissections in an effort to define ideal facial muscle targets for needle stimulation and corresponding topographic locations for lead placement. F1

Technical Details

After sterile preparation, a 2-cm midline incision was made over the larynx. The subcutaneous tissue, cutaneous coli, and sternohyoideus muscles were retracted, and a puncture was made within the cricothyroid membrane. The tracheostomy device was inserted through the membrane, and the surrounding tissues were closed securely around the device. Numerous stay sutures were placed bilaterally along the trachea with heavy silk to aid replacement if the tube were to become dislodged. Postoperative lateral cephalograms were taken to ensure proper positioning. After surgery, the tracheostomy tube was suctioned both on an hourly schedule and as needed. Feeding percutaneous endoscopic gastrostomy

TABLE 1. Advantages and Disadvantages of Pertinent Ancillary Procedures Applicable to Preclinical Craniomaxillofacial Investigation in Swine

Ancillary Procedure	Advantages	Disadvantages
Surgical airway		
Shiley tracheostomy	1. Easy to obtain 2. Relatively low cost 3. Surgeon familiarity	1. Inadequate spacing for thick subcutaneous tissue in swine 2. Rigid plastic throughout the appliance risking injury to the tracheal wall
Bivona tracheostomy	1. Accommodates large amount of subcutaneous at in swine neck 2. Can be ordered with various lengths depending on size and age of swine at the time of surgery 3. Metal-reinforced soft plastic reduces risk for airway collapse and tracheal wall necrosis/perforation	1. Requires custom order 2. Increased relative cost
Feeding access		
Esophagostomy	1. Relative low cost for red rubber catheter 2. Minimal time for insertion	1. Poorly tolerated by swine 2. Potential for kinking and malpositioning 3. Neck position is less than ideal for craniofacial research
PEG tube	1. Dependable and constant in function and position 2. Position away from neck and dorsal tunneling is ideal for craniofacial-specific research	1. Increased cost 2. Technically challenging 3. Requires 2-team approach
Intravenous access		
Cervical tunneled catheter	1. Cervical venous anatomy is constant 2. Neck region is clean 3. More difficult for large animal to chew when in posterior neck position	1. May interfere with craniofacial research involving jugular vein anatomy 2. If ventral, may be easily chewed or grasped by animal 3. Requires one to get close to the face at times of blood draw and intravenous administration (eg, risk for being bitten by animal)
Femoral tunneled catheter	1. Remains far from craniofacial surgical site 2. Once tunneled dorsally, it is easy to obtain access when animal is standing erect	1. Requires dorsal tunneling to avoid animal chewing 2. Femoral region is more likely to become infected with time

(PEG) tubes and tunneled femoral vein Hickman catheters were placed using standard technique.[11,14]

RESULTS

Overall, this study was challenging given the lack of published research in this field and is the overarching impetus for this publication. Most ancillary procedures now being used by our team have been T1 T2 improved after numerous practice sessions (Tables 1 and 2). After several swine cadaver/plastic model surgeries (n = 5), 3 live surgeries were completed to assist our engineering colleagues in developing a novel computer-assisted planning and execution (CAPE) system. All major dental, skeletal, and esthetic inconsistencies were overcome using the technology in light of a major size mismatch between donor and recipient.[4–6] However, all 3 face-jaw-teeth transplant recipients had premature death related to ancillary procedures, thereby demonstrating the need for further research.

The first swine recipient expired toward the completion of the procedure because of an airway-related complication as the final bone cuts were being made in preparation for transplantation. The second recipient survived the face-jaw-teeth allotransplant overnight but expired on postoperative day 1 because of complications surrounding the femoral intravenous catheter. This originated from inadvertent displacement and resulted in compartment syndrome/hind limb ischemia. On recovery, the animal demonstrated hind limb paralysis necessitating decompressive fasciotomy. Although urgent fasciotomy restored perfusion, the additional anesthesia was lethal, and the animal expired on postoperative day 1.

The third animal survived face-jaw-teeth transplantation but also expired on postoperative day 1. This premature death was related to a complication surrounding the PEG tube. At some point during recovery and moving the animal back into the cage, the PEG tube became dislodged. Soon thereafter, the swine expired on postoperative day 1 during anesthesia induction for revisional gastrostomy surgery. Of note, the transplant itself was technically successful with adequate perfusion at the end of the operation and assisted us greatly in gathering valuable data for our team's technology development. As expected, the face-jaw-teeth alloflap demonstrated gravity-related venous congestion. Efforts surrounding computer-assisted surgery and cutting guide modifications helped to improve reconstructive outcomes in both F2 the second and third live surgeries[4–6] (Fig. 2). In summary, all 3 perioperative complications (ie, central line, feeding tube, and airway obstruction) were independent of the actual face-jaw-teeth transplant (3/3, 100%).

Airway Experience

The first surgery used a standard Shiley tracheostomy as previously described.[9] However, intraoperatively, it was realized that the human Shiley appliance had a suboptimal fit, specifically due to the swine's large amount of subcutaneous fat and significant anterior-posterior distance from the skin to anterior trachea. Although it was

Fig 2 4/C

FIGURE 2. Photograph of swine on postoperative day 1 after Le Fort-based facial transplant. Custom Bivona tracheostomy being well tolerated while ambulating. Maxillofacial transplant is viable on examination with gravity-related congestion. This animal expired prematurely because of a complication surrounding PEG tube dislodgement.

possible to ventilate the swine with positive pressure under general anesthesia, the inadequacies of the standard-sized human tracheostomy manifested themselves when the swine began to awaken and flex/extend its neck.

The swine trachea is different from humans—it is angulated and does not run parallel to the external neck as expected. It courses deeply toward the thorax at a more obtuse angle away from the external neck. Moreover, the axis of neck flexion in the swine is more inferior as compared with a human and, in this case series, in relatively close proximity to the tracheostomy site. This may result in frequent pressure of the rigid device against the posterior tracheal wall during extreme neck movements. In this particular face transplant model, the infraorbital nerve is divided during harvest of the face-jaw-teeth alloflap. This results in diminished midfacial sensation, which may lead to forceful head movements against the cage for assistance with proprioception. As such, a swine with a firm human Shiley appliance may be at high risk for posterior tracheal wall necrosis due to repetitive neck rotation (Fig. 3). F3

Moving forward, we switched to an extra-large Shiley tracheostomy appliance (Covidien Shiley, Mansfield, MA) (common size used for a morbidly obese patient) with an increased length and more obtuse curvature. It was hypothesized that the increased anterior-posterior distance between the flange and cuff and the overall length would help to accommodate the increased amount of subcutaneous tissue (Fig. 4). F4 Despite being of appropriate length and angle, the rigidity of the plastic tubing was again suspicious for posterior tracheal wall necrosis. Therefore, we changed to a soft, wire-reinforced, noncompressible, plastic Bivona custom order appliance (Smiths Medical, Dublin, OH) (Fig. 5). This modification proved efficacious and, to date, remains F5 our preferred option for perioperative airway management (Supplemental Digital Content, video, http://links.lww.com/SCS/A86).

Feeding Tube Experience

The original plan was to use an esophagostomy tube based on reports related to ease of placement and low rate of complication.[10]

TABLE 2. Number of Animals Studied Per Ancillary Procedure

Procedure	Number of Animals, n
Standard Shiley tracheostomy	1
Extra-large Shiley tracheostomy	1
Bivona tracheostomy	4
Esophagostomy	1
PEG tube	5
External jugular tunneled catheter	4
Femoral tunneled catheter	2
Laser angiography	4

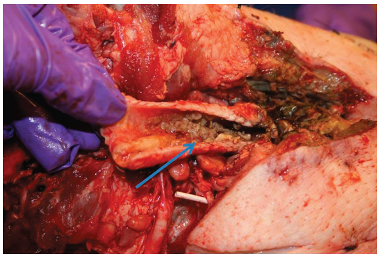


Fig 3 4/C

FIGURE 3. Posterior tracheal wall necrosis found during necropsy after using standard Shiley tracheostomy (blue arrow).

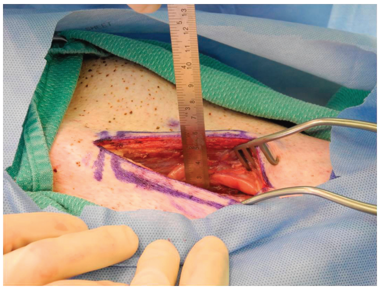


FIGURE 4. Challenging tracheostomy insertion due to increased amount of subcutaneous tissue with skin-to-trachea distance around 6 cm.

During the first experiment, a red rubber catheter was placed for esophageal access through a lateral stab incision. The 14F catheter was passed along the lateral neck down within the esophagus and sewn securely into position. However, upon recovery from anesthesia, the animal began to cough repeatedly with force, and the tube became retroflexed through the mouth (rather than descending distally within the esophagus toward the stomach). Therefore, for the next surgery, we switched to a PEG tube. This was placed using a pediatric endoscope and seemed straightforward and well tolerated by the swine (n = 5). Vigilance is required to maintain proper PEG tube positioning, and therefore, our team advises the chronic use of a protective jacket (Fig. 6).

Femoral Intravenous Line Experience

On the basis of our laboratory's experience with swine hind limb transplantation, a tunneled Hickman intravenous catheter was selected first and placed within the external jugular vein (Fig. 7). The dorsal tunneling was effective in preventing self-induced trauma by the swine.[11] However, as the Le Fort-based facial alloflap was being designed, it was noted that the alloflap's inflow/outflow design and necessary anastomoses were dependent on the neck's venous drainage system. Therefore, all other options were considered including the subclavian and/or femoral veins. After careful consideration, the femoral vein was selected in an effort to preserve the head and neck venous drainage system (Fig. 8). Femoral lines have several drawbacks including the need for a longer tunneling distance (from groin to dorsum as compared with from neck to dorsum). Subcutaneous tunneling is mandatory because groin catheters are at risk for

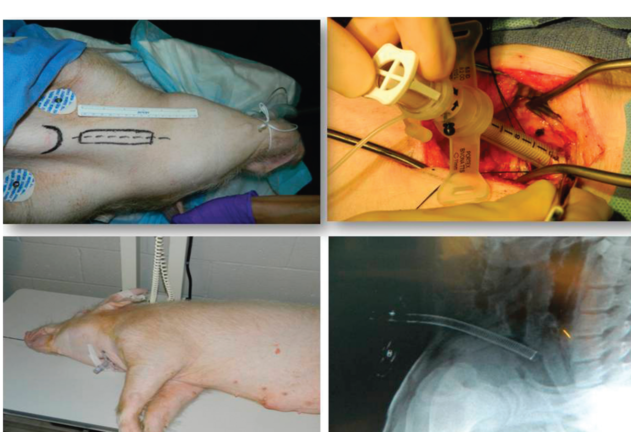


FIGURE 5. Intraoperative markings for Bivona tracheostomy placement (top left), actual placement with bilateral tracheal stay sutures in place (top right), animal on x-ray table after completion (bottom left), and final x-ray confirming acceptable placement (bottom right).

FIGURE 6. PEG tube placement by 2-surgeon team (top center), fiberoptic pediatric endoscope inserted and fundus location is visualized with abdominal wall transillumination (bottom left), and PEG tube being sewn securely to the abdominal wall (bottom right).

kinking during ambulation and remain vulnerable to damage or removal by the animal (ie, chewing).

Laser Angiography Experience

The SPY Intraoperative Perfusion Assessment System (LifeCell Corp, Branchburg, NJ) allows monitoring of tissue perfusion and venous outflow using intravascular injection of the fluorescent dye indocyanine green and visualization with a near-infrared laser.[12] For the Le Fort-based, face-jaw-teeth alloflaps, perfusion of both hemifaces was present on 3 consecutive occasions. Most importantly, the snout being the farthest area from the pedicle showed perfusion from bilateral pedicle inflow (Fig. 9).

Facial Electromyoneurography Experience

A half-face dissection was performed to identify the surface landmarks corresponding to the underlying facial musculature and for topographical assessment of ideal needle electrode placement (Fig. 10). Both surface and percutaneous electrodes were studied. An ADInstruments electrophysiology system (Colorado Springs, CO) was used to assess compound muscle action potential recordings over time in hopes of establishing a protocol for assessing neuromuscular recovery after maxillofacial allotransplant. Compound muscle action potentials were recorded preoperatively from snout musculature of the donor/recipient swine using percutaneous needle electrodes after stimulation of the facial nerve trunk (Fig. 11). This taught us that

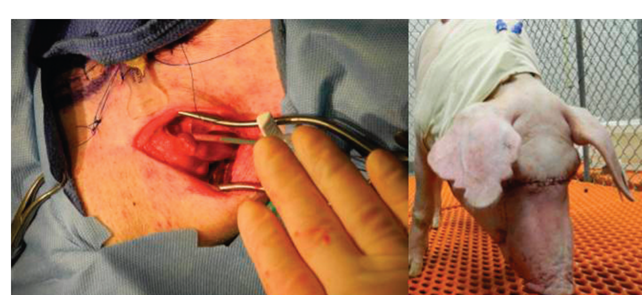


FIGURE 7. Hickman catheter inserted into the left external jugular vein (left) and tunneled dorsally with protective wrap in place (right).

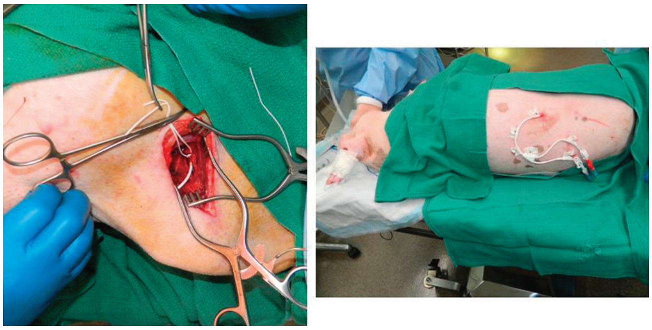


FIGURE 8. Right femoral Hickman catheter placed (left) and then tunneled dorsally with skin-level stay sutures (right).

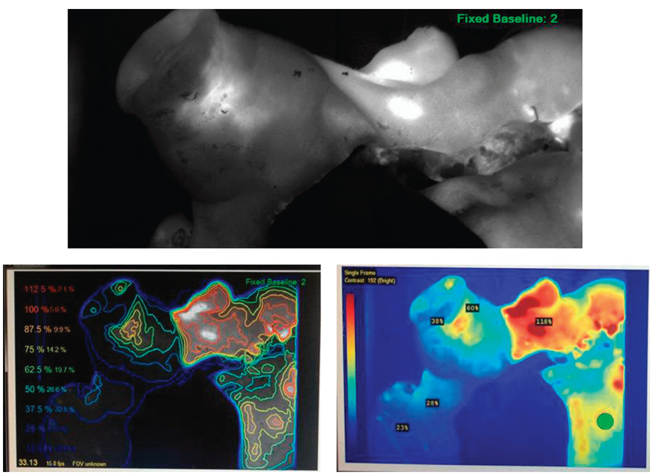


FIGURE 9. Near-infrared laser angiography showing perfusion to snout. Left-sided neck vessels have been divided in preparation for transplant (top center). Quantitative analysis image (bottom left) and color depictions are also shown for direct correlation (bottom right).

the depressor rosti, depressor labi superioris, and labial depressor muscles are best stimulated in a location along the oral commissure —as a means of testing the buccal branch of the facial nerve.

DISCUSSION

Basic science research draws from a variety of avenues including both small and large animals.[13,15–20] However, in order for surgeons and biomedical engineers to collaborate, develop, and enhance futuristic modalities related to computer-assisted technology, larger-scale anatomy is required. Therefore, researchers looking to improve outcomes in craniofacial surgery should be encouraged to first assess safety and reliability of new techniques in large animal laboratories[4–6] (Fig. 12).

FIGURE 10. Half-face facial dissection showing placement of electrode into depressor labi superiorus and depressor rosti muscles.

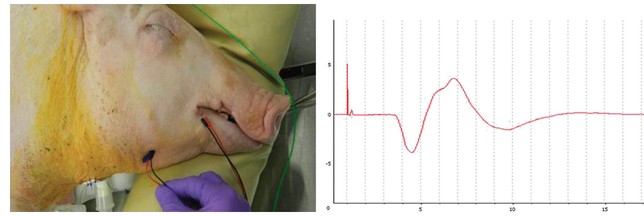


FIGURE 11. EMG of the right facial nerve in swine being performed (left) and simultaneous tracing (right).

Because of the numerous reasons noted throughout the literature, those planning to engage innovative developments in craniomaxillofacial surgery are likely to choose swine (Table 3).[21–23] Similarly, our laboratory was able to develop a preliminary platform, referred to as a CAPE system[4–6] with full translational capabilities (Fig. 13). Although cadaveric swine and human surgeries were advantageous in the beginning, the live swine surgeries (n = 3) were much more revealing to the engineers and nonphysicians with respect to preclinical expectations and acquiring knowledge/insight related to dynamic musculoskeletal impedance.

Rigor mortis, found in all cadavers (human and swine), limits real-time assessment of obstacles related to the masticatory muscles, which are pertinent in many areas of craniomaxillofacial surgery including face-jaw-teeth transplantation. It behooves the craniofacial researcher to learn from our experience presented here. As expected, our successes and failures have required an exorbitant amount of time, energy, manpower, and grant funding, and therefore, it is incumbent to share these experiences for the betterment of the specialty.

The welfare of all laboratory animals remains top priority, and thus, developing these ancillary procedures in the future will ultimately improve safety. Swindle[21] writes that "a successful tracheostomy can be placed in the dorsal recumbent position at the preferred level of the cricothyroid membrane" in swine. However, there are no descriptions of the appliance chosen and/or guidance on proper size or length, which may be because this type of survival surgery has not yet been attempted. There are also no recommendations on long-term maintenance of tracheostomies, no warnings of tube rigidity in swine, and no mention of the tube's propensity for tracheal wall necrosis in the setting of orthotopic Le Fort-based, maxillofacial transplant investigation.

Postoperative airway management for craniofacial research is paramount. It was found that continuous suctioning of the tracheostomy with gentle irrigation was required on an hourly basis to prevent obstruction from thick secretions. Unfortunately, inner cannulas are

FIGURE 12. Frontal view of swine recipient after successful orthotopic Le Fort-based, maxillofacial transplantation as similar to humans. Microvascular anastomoses have been completely bilateral in the neck in addition to bilateral facial nerve reconstruction.

Fig 13 4/C

FIGURE 13. Plastic models are used preoperatively for the development of innovative strategies related to CAPE system, which has been shown to optimize skeletal alignment, esthetic harmony, and dental relation in the setting of a large size-mismatch discrepancy between donor and recipient.

TABLE 3. Advantages of Using Swine as a Translational Model for Le Fort-Based, Maxillofacial Transplantation and Various Other Areas in Craniomaxillofacial Surgery

• Ideal relationship between pterygoid plates, palatine bones, and maxillary tuberosities as compared with human skull
• Quick growth of the swine's craniomaxillofacial skeleton with the head size reaching maturity at around 8 months
• Bone turnover is equal to humans making the swine critical for bone healing experiments
• Chewing pattern and transmission of the masticatory forces are similar to humans
• Large circulating blood volumes allow for more complex surgeries as opposed to smaller animals
• Massachusetts General Hospital swine are uniquely available as a swine leukocyte antigen-defined breed, which is ideal (versus other large animals, ie, dogs, nonhuman primates, sheep) for preclinical research in vascularized composite and solid organ transplantation

not currently available on custom tracheostomies. Animal caretakers must also be well familiarized with techniques for suction clearance in an emergency. A strong portable suction machine should be kept near the swine's cage in the event of mucous plugging. One should also be familiar with human tracheostomy protocols because this particular area is lacking significant research.[24]

Fig 14 4/C

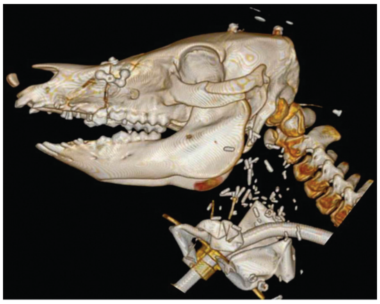


FIGURE 14. Three-dimensional CT scan demonstrating optimal skeletal alignment and dental relation status after face-jaw-teeth transplant in the setting of a large size-mismatch between donor and recipient. Custom Bivona tracheostomy is also seen in position.

Fig 15 4/C

FIGURE 15. Left-sided oblique intraoperative views of a Le Fort-based, maxillofacial transplant completed in a live swine recipient (left) and human cadaver recipient (right).

As for postoperative nutrition, Bollen et al[22] recommend direct gastric intubations for both medicine and nutritional delivery. Although this seems viable, research such as ours would require daily sedation for postoperative feeds for weeks/months, which is simply not feasible. Hooda et al[23] support the use of parenteral amino acid therapy via a central line catheter. Although reasonable, this method adds significant cost and labor. As such, we consider the PEG tube to be most appropriate—in that it provides the ideal route for enteral nutrition irrespective of the level of facial transplantation being studied.[6] However, one must be aware that inadvertent dislodgement in the perioperative setting can quickly lead to death. As such, we recommend that well-fitting laboratory jackets be worn at all times (Fig. 2).[22]

Long-term intravascular access for drug administration and blood sampling is also challenging. Lombardo et al[26] reported success with long-term 11F jugular catheters in swine with a low incidence of infection and thrombosis. However, in craniofacial surgery, the external jugular vein/carotid artery anatomy are pertinent for regional perfusion and free tissue transfer anastomoses, thereby making this option less favorable.[5,27,28]

The use of near-infrared laser angiography was found to be critical for flap design given the swine's skin thickness and played a vital role in preoperative planning and intraoperative assessment.[11] Although the vascular network of a human's face is well described and understood, the arterial and venous descriptions of a swine's face are poorly detailed. One valuable finding from this study was the determination of a "reversed facial-skeletal ratio" in swine versus humans. The "maxilla-to-face ratio" for swine was determined to be much greater and in reverse relation when compared with humans. This is most likely due to the fact that swine have prominent maxillary tuberosities, as compared with humans who have relatively larger faces and smaller maxillae and rely therefore much less on their nose (eg, snout) for feeding and protection (Fig. 14). F14

For research like ours related to face-jaw-teeth transplantation, these findings are critically important, because those seeking to create a new craniofacial model in swine may assume the common facial artery/vein pedicle design to be feasible (as is most commonly used

Fig 16 4/C

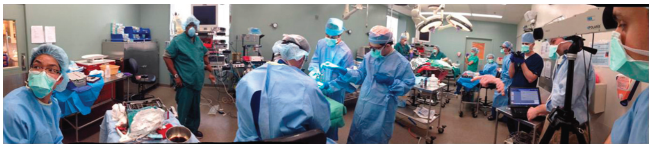


FIGURE 16. Panoramic, intraoperative photograph demonstrating the use of surgical navigation on the near side in conjunction with novel CAPE system. On the far right side, the engineering team from the Johns Hopkins University Applied Physics Laboratory uses a laptop computer and Polaris camera for immediate surgeon feedback. This type of complex surgery requires 2 large surgical teams working simultaneously, as identical to human facial transplantation.

Fig 17 4/C

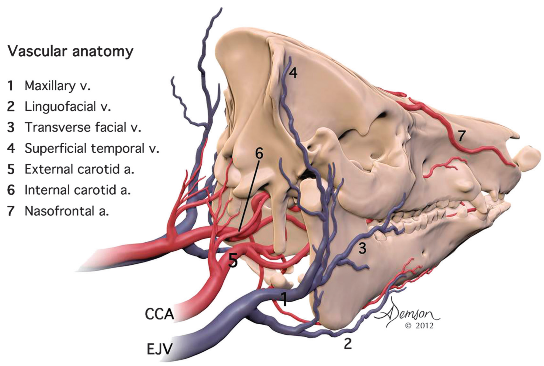


FIGURE 17. Illustration depicting the complex three-dimensional vascular anatomy of a swine's craniofacial skeleton.

worldwide for human facial transplants).[29,30] However, facial alloflaps designed solely on the facial vessels in swine will fail because of their small caliber. Because of the aforementioned "face-to-maxilla" ratio imbalance, the swine's internal maxillary vessels are consistently larger, and the internal system is much more pertinent for swine facial transplantation. These findings were also elucidated by laser angiography and have allowed us to design an orthotopic maxillofacial transplant model for translational investigation.[4–6]

Our experience with facial electromyoneurography (EMG) testing in swine was "eye-opening." With no available literature, it was difficult to proceed for several reasons including skin thickness and disproportionate facial muscles (as compared with humans). By completing half-face skin dissections, we found the percutaneous electrodes to be more valuable and effective.

This study was able to decipher an ideal location for facial muscle input—just lateral to the oral commissure within the lip depressors, which are innervated by the buccal branch (Fig. 10). One main drawback of facial EMG is its requirement for general anesthesia, which adds significant time and expense. However, for the specialty of craniofacial surgery, such as elucidating patterns of facial nerve recovery status after transplantation,[31] this may be worthy
AQ4 and justifiable when coordinated with CT scanning evaluation.

One weakness of this study is its retrospective design and small number of surgeries. However, large quantities and statistical comparison of ancillary procedures would be impractical considering the necessary time, funding, and manpower needed for this type of experiment. We therefore feel that, by learning through experimentation and adjusting with each success and failure, one is able to succeed in an area with very little precedence. The goal is to share these valuable lessons with the craniofacial research community so as to facilitate further large animal experiments in Le Fort-based, maxillofacial transplantation.[31–33]

CONCLUSIONS

The facial skeleton is responsible for providing one's appearance and identity, unlike its overlying soft tissues, and therefore, previous animal models evaluating soft tissue-only face transplants will not provide the necessary insight to advance this field. Also difficult is that preclinical craniofacial research lends itself to high complications given its close relation to the nose, mouth, trachea, esophagus, and brain. Therefore, it is imperative that all research teams become experts with ancillary procedures related to airway management, feeding tube placement, and central line access. Each one should be practiced by a consistent team of dedicated personnel. Constant collaboration and communication between an experienced craniofacial surgeon and veterinarian staff member is critical for the welfare of the animals and the project's long-term success. Particular emphasis should be given to protective garments and stay sutures, because tube dislodgement and/or device malpositioning may jeopardize animal survival.

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Appendix 1

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Modeling the biomechanics of swine mastication – An inverse dynamics approach

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ABSTRACT

A novel reconstructive alternative for patients with severe facial structural deformity is Le Fort-based, face-jaw-teeth transplantation (FJTT). To date, however, only ten surgeries have included underlying skeletal and jaw-teeth components, all yielding sub-optimal results and a need for a subsequent revision surgery, due to size mismatch and lack of precise planning. Numerous studies have proven swine to be appropriate candidates for translational studies including pre-operative planning of transplantation. An important aspect of planning FJTT is determining the optimal muscle attachment sites on the recipient's jaw, which requires a clear understanding of mastication and bite mechanics in relation to the new donated upper and/or lower jaw. A segmented CT scan coupled with data taken from literature defined a biomechanical model of mandible and jaw muscles of a swine. The model was driven using tracked motion and external force data of one cycle of chewing published earlier, and predicted the muscle activation patterns as well as temporomandibular joint (TMJ) reaction forces and condylar motions. Two methods, polynomial and min/max optimization, were used for solving the muscle recruitment problem. Similar performances were observed between the two methods. On average, there was a mean absolute error (MAE) of <0.08 between the predicted and measured activation levels of all muscles, and an MAE of <7 N for TMJ reaction forces. Simulated activations qualitatively followed the same patterns as the reference data and there was very good agreement for simulated TMJ forces. The polynomial optimization produced a smoother output, suggesting that it is more suitable for studying such motions. Average MAE for condylar motion was 1.2 mm, which reduced to 0.37 mm when the input incisor motion was scaled to reflect the possible size mismatch between the current and original swine models. Results support the hypothesis that the model can be used for planning of facial transplantation.

1. Introduction

Le Fort-based, face-jaw-teeth (craniomaxillofacial) transplantation (FJTT) is a challenging procedure during which both hard and soft tissues taken from a cadaveric donor replace damaged portions of a recipient's face and underlying skeleton. A variety of different parameters need to be considered to obtain an optimal outcome for this type of surgery, including aesthetics and cephalometric measures in relation to donor-to-recipient discrepancies, as well as optimum teeth occlusion (Gordon et al., 2011, 2012). Computer-assisted systems that use patient-specific models can provide the necessary tools for surgical pre-operative planning with the salient features of the outcome in mind. We have recently reported the results of our computer-assisted planning and execution (CAPE) system for FJTT surgery that uses pre-operative CT scans and planning along with optical tracking and custom-made guides to help the surgeon perform the transplantation (Gordon et al., 2013, 2014).

An important aspect of a FJTT surgery is that it requires precise planning to determine the expected changes related to masticatory muscles affecting both lower and upper jaws, the relationship between which could be different than that of the healthy recipient. The new occlusal plane angle, dento-facial relationships, and muscle insertions directly affect the way muscles are recruited for providing forces and motions for chewing or biting. Previous studies have identified swine as having analogous facial skeletal structures and actions of mastication compared to humans. Therefore, these characteristics make swine the ideal candidate for

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translational investigation of FJTT (Al Rakan et al., in press; Farkas et al., 1976, 1977; Papadaki et al., 2010; Santiago et al., 2014; Strom et al., 1986). However, further understanding of swine mastication and improved opportunities for translating the swine FJTT model to humans requires reliable models of swine jaw biomechanics (Hannam, 2011).

Modeling human masticatory biomechanics has been the subject of extensive research. A majority of the computational models incorporate forward dynamics where muscle activations or forces are the known input and the resulting mandibular motion and the temporomandibular joint (TMJ) reaction forces are computed as the output (Stavness et al., 2006). While useful for estimating outcomes such as mandibular motion or maximum bite force, this approach has the drawback of relying on the availability of individual muscle activations, which are difficult or impossible to acquire from every individual subject. Solving the inverse problem, on the other hand, can help better guide the FJTT reconstruction. A very important case is when the patient is missing one or more key masticatory muscles and thus the normal mandible motion and bite force have to be restored with a subset of original activators. This type of injury is commonly seen in wounded warriors and/or civilians with close-range, ballistic injuries to the face, head, and neck (Lew et al., 2010). Inverse dynamics can help identify muscle attachments so that, for a typical biting or chewing motion and force, muscle activations and/or TMJ reaction forces are minimized. In addition, solving the inverse problem can give insights regarding the working of the central nervous system (CNS) for either healthy individuals or patients with facial deformities (de Zee et al., 2007; Stavness et al., 2010).

The inverse dynamics problem deals with finding muscle/joint forces/torques, given the motion and external forces. Generally, solving the inverse problem is computationally less expensive than forward simulations, since motion (position and its derivatives) can be directly plugged into the equations of motion and the resultant joint forces can be computed without any need for integration over time (Erdemir et al., 2007). Finding individual muscle's contributions to the resultant forces, however, requires optimization, since most joints are redundantly activated, i.e., usually more than one muscle spans a joint. Two major groups of such solvers are forward dynamics-assisted and static optimizers. In the former, a set of initial muscle activations is used for solving the forward dynamics problem and the resulting motion and/or external forces are compared with the reference data. The optimizer then adjusts the muscle patterns so that the error is minimized (Koolstra and van Eijden, 2001; Hannam et al., 2008). In the latter, at each simulation time step, an optimization problem is solved that, based on muscle efforts, minimizes a (physiologically-related) function. Condylar joint load or muscle fatigue are among the popular such objective functions (Koolstra et al., 1988; May et al., 2001; Osborn and Baragar, 1985). This approach is computationally inexpensive and can be used for various sensitivity analyses (Erdemir et al., 2007) including optimizing muscle attachment sites for planning of FJTT surgery. Among other notable methods of optimization in masticatory dynamics is the method of Dynamic Geometric Optimization (DGO) used by Curtis et al. (2010) where muscles were activated based on their lines of action with respect to a specific tracked target point on the mandible of a lizard. They found good agreement between the results of their two dimensional simulations and electromyography (EMG) signals. A good review of the state of the art of masticatory biomechanics modeling is done by Curtis (2011).

Recently there have been efforts in creating software solutions dedicated to forward or inverse dynamics simulations of biomechanical motions, including masticatory dynamics. These include open-source platforms such as ArtiSynth (Lloyd et al., 2012) and OpenSim (Delp et al., 2007), and commercial software such as AnyBody (Damsgaard et al., 2006). These have shown various levels of success in performing inverse dynamics analyses and predicting muscle patterns for human mastication (Stavness et al., 2010; Cadova and Gallo, 2013; de Zee et al., 2007), with the study of de Zee et al. the only one, to our knowledge, that included direct quantitative comparison between measured and predicted activation patterns. A similar inverse analysis of swine mastication is, however, missing from the literature. Therefore, as a first step in planning FJTT for swine subjects, we created a biomechanical model of jaw and mastication, and used the simulation results of previous forward dynamics models to drive and verify the model. The following sections describe the model and the simulation as well as the results and their comparison with the reference data. A discussion about the implications of the model concludes the paper.

2. Methods

A musculoskeletal model of a swine skull, mandible and the mastication muscles was created using the proprietary software AnyBody (AnyBody Technology, Aalborg, Denmark). The model included bilateral jaw closers and openers as follows: superficial and deep masseter, anterior, medial, and posterior temporalis,

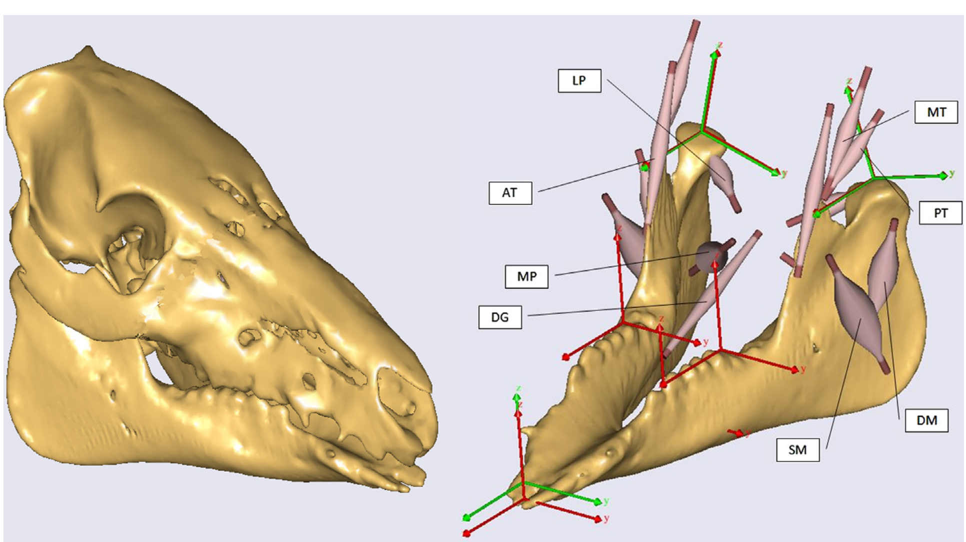

Fig. 1. Graphical representation of the skull (left) and mandible and muscle attachments with the skull hidden (right). Muscle abbreviations are as follows: superficial (SM) and deep (DM) masseter, anterior (AT), medial (MT), and posterior (PT) temporalis, medial (MP) and lateral (LP) pterygoid, and digastric (DG). Coordinate frames represent the TMJs, first molars, and lower and upper incisors. Red frames are attached to the mandible (moving body) and green frames are attached to the skull (fixed body). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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medial and lateral pterygoid, and digastric, resulting in a total of 16 muscles (Fig. 1). This arrangement was taken from the simulation studies of Langenbach et al. (2002, 2006). Manual segmentation using commercial image processing software (Amira, Visualization Sciences Group, Burlington, MA; Mimics, Materialise, Plymouth, MI) defined surface representations of a 15 kg miniature swine from computed tomography (CT) data. A SOMATOM Definition Flash scanner (Siemens Healthcare, Germany) obtained the CT data at a resolution of $0.45\times0.45\times0.60\ \mathrm{mm}^3$. The musculoskeletal model included a rigidly fixed skull and a freely moving mandible. Modeling of the two TMJs follows that described by de Zee et al. (2007) – the two TMJ points on the mandible were constrained to translate on a slanted plane, representative of the mandibular fossa, and both TMJs were free to rotate in all directions. This left the mandible with four degrees of freedom (DOFs). By analyzing the segmented surface representation of the mandible, the plane defining the TMJ motion was canted 15° medially (Zhang, 2001). The inter-condylar distance was the same as that of the original study (72 mm).

Muscles were modeled as Hill-type actuators (Zajac, 1989). Peak isometric forces were taken from the study of Langenbach et al. (2002), and the attachment sites were determined based on anatomical landmarks and published swine dissection studies (Herring and Scapino, 1973; Herring et al., 1984). Since the literature is limited regarding actual fiber/tendon ratios for most of swine mastication muscles, we defined 90% of the total muscle length at jaw close as optimum fiber length and the remainder as slack tendon length. This resulted in numbers similar to optimum lengths reported by Anapol and Herring (1989) for digastric and masseter. At 5% tension, each muscle's tendon was assumed to provide a passive force equal to the maximum isometric fiber force (Langenbach et al., 2002). Muscle parameters are summarized in Table 1.

To prescribe motion and external forces, lower incisor and the bilateral first molars were manually identified on the surface model (Fig. 1). The model was driven by the three DOF motion of the lower incisor recorded by Langenbach et al. (2002) as the output of their simulation (Fig. 2). The remaining free DOF of the mandible was restricted by prohibiting the right (working) TMJ from lateral motion. Food crushing and teeth occlusal forces were also applied on the working side first molar (Langenbach et al., 2006). Mass and inertia of the mandible were set according to the reference study (Langenbach et al., 2002). Center of mass was assumed as the geometrical center of the mandible surface model and the whole model was subjected to gravity in the vertical direction. The software then calculated the muscle activations and TMJ reaction forces as well as condylar motions in the anterior–posterior (A–P) direction. We examined following two methods of forming the optimization problem: 3rd order polynomial (Crowninshield and Brand, 1981) and min/max (Rasmussen et al., 2001) muscle recruitment algorithms. The optimization problem can be summarized as

$$\min g(F_i)$$
$$\text{s.t.}\quad C\mathbf{f}=\mathbf{r}$$
$$0\le f_i\le N_i,\quad i=1\ldots m \tag{1}$$

Here $f_i=aN_i$ is each muscle's force, N_i is the muscle instantaneous strength (the maximum force muscle can provide at its current configuration if it is maximally excited), a is activation ($a\in[0,1]$), $\mathbf{f}$ is the vector of muscle and joint forces acting on the moving body (mandible), $\mathbf{r}$ is a vector representing the external and inertial forces, C is a matrix of coefficients, and m is the number of muscles moving the rigid body. The first constraint essentially ensures that the equations of motions hold for the rigid body. In the case of polynomial optimization, the objective function $g(F_i)$ can be written as

$$g(F_i)=\sum_{i=1}^{m}\left(\frac{F_i}{N_i}\right)^3,$$

while for the min/max problem, the objective function takes the form

$$g(F_i)=\max\left(\frac{F_i}{N_i}\right),\quad i=1\ldots m.$$

Simulated activation signals were compared with the reference data of Langenbach et al. (2002). For their study, they used indwelling wire electrodes to record EMG activities of mastication muscles and then fitted B-spline curves to the results. Comparison between those data and our simulation was performed by finding the mean absolute error (MAE) as proposed by de Zee et al. (2007) using

$$\mathrm{MAE}=\frac{1}{n}\sum_{i=1}^{n}|S_i-M_i| \tag{2}$$

Here M is the measured signal, S is the simulated signal, and n is the number of samples. The original study (Langenbach et al., 2002) reported only one set of activations for the temporalis muscle bundles so we averaged the simulated activation of the three temporalis muscles to compare with the reference data. The same method was used to compare the TMJ reaction force and A–P condyle motion profiles. Upon primary inspection, the A–P condyle motions deviated from the original simulation during jaw opening and we hypothesized a size mismatch to be the source of discrepancy. Therefore, the simulation was repeated with incisor motion that was scaled to 60% its original values and the A–P motion was recorded again.

Table 1
Muscle parameters.

Muscle	Optimum fiber length (cm)	Maximum force at optimum length (N)
Superficial masseter	5.4	304.4
Deep masseter	3.8	188.8
Anterior temporalis	5.0	64.8
Medial temporalis	3.9	73.2
Posterior temporalis	2.9	73.2
Medial pterygoid	3.4	226.8
Lateral pterygoid	2.9	100.4
Digastric	5.5	56.4

3. Results

Fig. 3 shows comparisons between the muscle activation patterns and Table 2 summarizes the MAE values. The average MAE was 0.077 (0.027–0.138) for polynomial and 0.074 (0.026–0.124) for min/max recruitment. All activations were sampled at 1 ms intervals. Similar qualitative patterns of activation can be seen between simulations and reference data for both recruitment methods, although min/max criteria produced some irregularities, e.g., for lateral pterygoid and digastric muscles. There was no statistical difference between left and right MAE results for either method ($P>0.79$).

Fig. 4 depicts the comparison between the working and balancing side TMJ reaction forces. Very good overall agreement for the patterns can be observed. The average MAE was 6.6 N in polynomial and 6.4 N in min/max optimization. The min/max

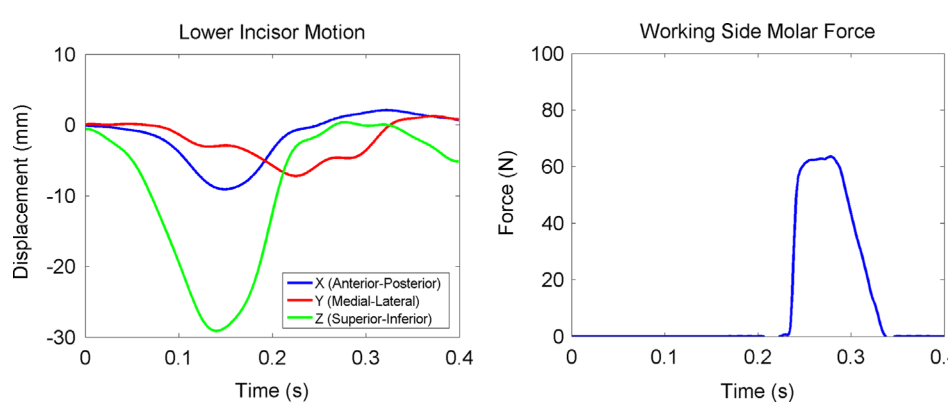

Fig. 2. Left: three-dimensional motion of the lower incisor. Right: external load (i.e., bite force) acting on the working side first molar.

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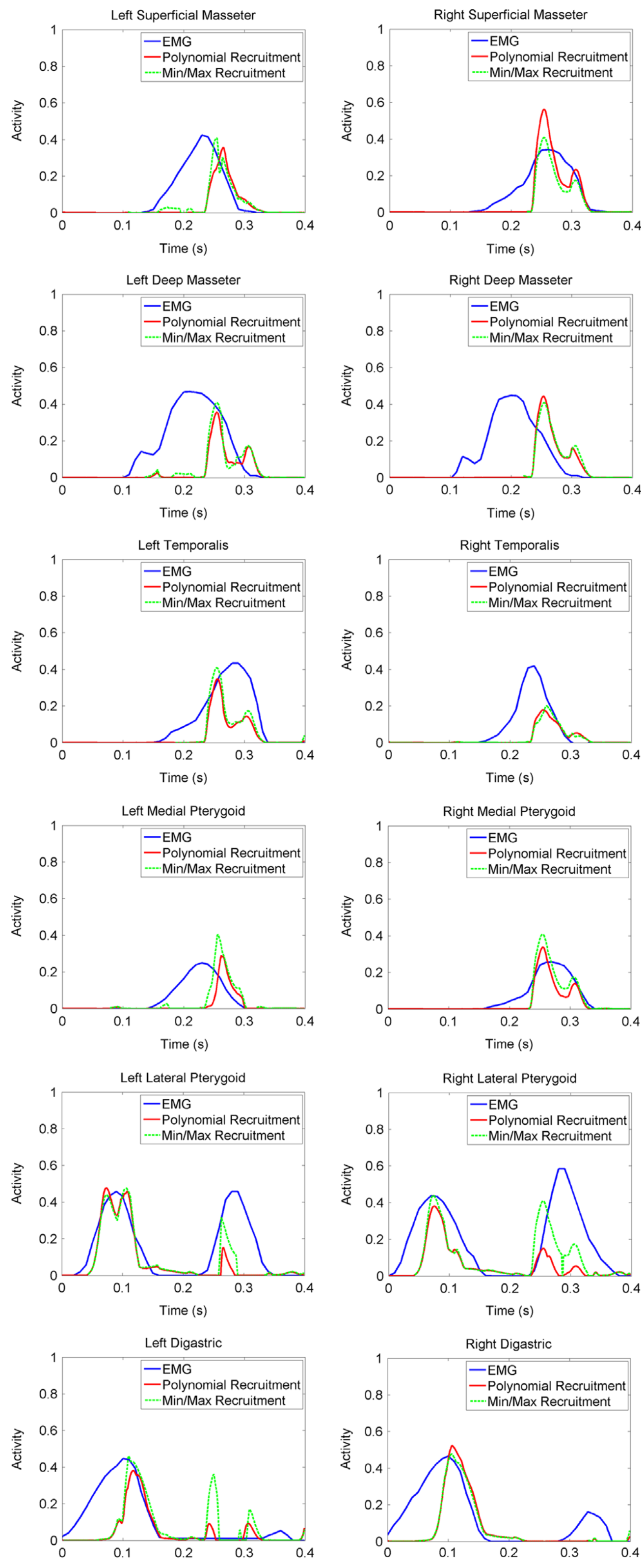

Fig. 3. Simulated and reference (EMG) activation profiles.

method resulted in a spike in TMJ reaction force for the left side, while polynomial optimization created smoother profiles in general.

Fig. 5 shows the reference and simulated condylar motions. When unscaled data was used, the average MAE for two sides was 1.2 mm (maximum 3.98 mm), which reduced to 0.37 (maximum 1.19 mm) when the incisor motion was scaled.

Table 2
Mean absolute error for the muscle activations. Simulated activations of anterior, medial, and posterior temporalis muscles were averaged and compared against the reference data. Poly and min/max refer to polynomial and min/max recruitment algorithms, respectively.

Muscle	Left		Right	
	Poly	Min/Max	Poly	Min/Max
Superficial masseter	0.070	0.063	0.042	0.04
Deep masseter	0.115	0.112	0.113	0.113
Temporalis	0.065	0.062	0.050	0.049
Medial pterygoid	0.048	0.049	0.027	0.026
Lateral pterygoid	0.089	0.081	0.138	0.124
Digastric	0.075	0.088	0.090	0.086
Mean	0.077	0.077	0.076	0.073

4. Discussion

Effective planning of FJTT requires a deep understanding of the underlying biomechanics of mastication. In the single-jaw scenario, i.e., transplantation of maxilla only, the hybrid combination of donor and recipient jaw-teeth segments will undoubtedly have significant discrepancies with premature interference. For instance, all single-jaw recipients performed to date have required some form of major revision surgery due to significant malocclusion (Gordon et al., 2011, 2012). Reliable subject-specific biomechanical models may help plan such procedures through an understanding of the optimum muscle attachment sites and, ultimately, improve functional outcomes. Validating an inverse dynamics musculoskeletal model is a major undertaking and the several simplifying assumptions result in deviations from real scenarios. However, even when simplified, biomechanical models can provide valuable insights regarding the effect of muscle attachments on the outcome of the motion being studied.

In this paper we describe a musculoskeletal model of swine mastication containing several key jaw muscles. As a first verification step, the model was driven using the output of previous forward dynamics simulations (lower incisor motion and bite reaction forces) with the goal of predicting the simulation inputs (muscle activation levels) as well as TMJ reaction forces. Results showed good agreement for muscle recruitments with some discrepancies that could be related to the inevitable differences between the reference and the current model.

Among the likely sources of error could be the assumed muscle/fiber ratios that differed with the unknown ones of the reference simulations. We used a constant fiber/tendon length ratio for consistency and it is not currently known to us how manual adjustments to each individual muscle can improve the results. Nonetheless, the possibly improved ratios must be verified against experimental data of swine dissections. Also, muscle attachment points were found using anatomical landmarks on the surface representation and it is likely that the reference swine model had a different anatomy. Another source of error introduced into the model is the result of inaccuracies and noise in digitizing the motion plots that were used to drive the model. Since position data is differentiated twice to estimate accelerations and find forces, small inaccuracies can result in considerable deviations from the source data.

During the opening phase, digastric muscles in our model were activated later than the ones in the reference data. Also, in the reference simulations, jaw closers were activated quicker during the upward movement of the mandible. Besides the possible

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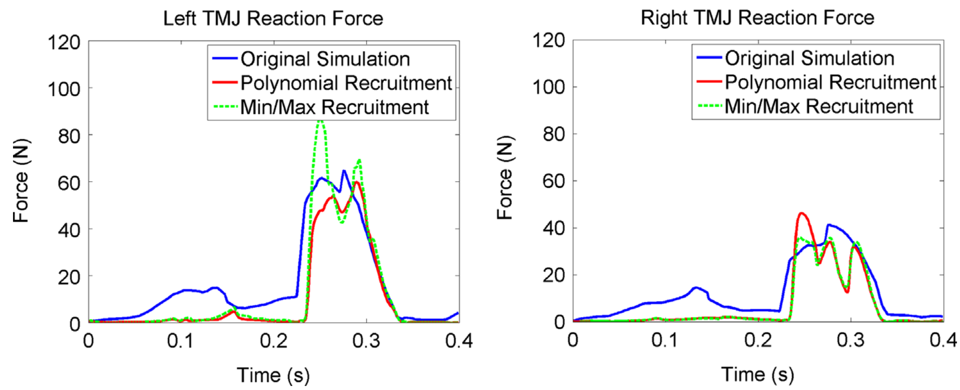

Fig. 4. Comparisons between the results of original (Langenbach et al., 2006) and current simulations of TMJ reaction forces.

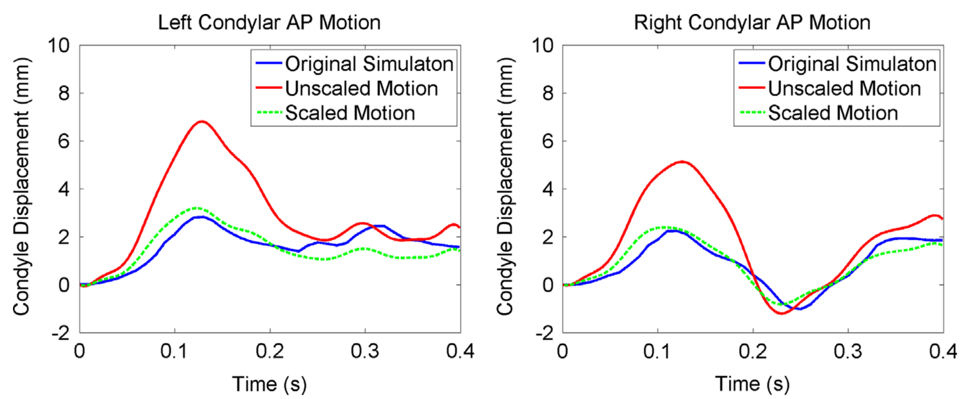

Fig. 5. Comparisons between the results of original (Langenbach et al., 2002) and current simulations of A–P condyle motions. “Unscaled Motion” represents the results of using the original digitized incisor motion while “Scaled Motion” denotes the results of simulation using the 60% scaled incisor motion.

differences in the jaw accelerations and center of mass locations, the force distributing algorithm in our simulation may have worked in a different way than the motor control system in the animal subject of the reference model. The lower jaw is one of the most redundantly mobilized joints in the body and the activating strategy of the central nervous system (CNS) for it is not completely understood. The simulations minimized the relative muscle force at each time step, which implies reduction of fatigue (Rasmussen et al., 2001). Although this has been shown to produce results that agree with biological data, in some human subjects/tasks, minimization of joint load has been shown to perform better (Iwasaki et al., 2003). Furthermore, gravity, seemingly, provided a large portion of the initial load required to open the jaw in the simulation and also the passive tension in the jaw closers contributed to pulling the mandible back up. This is in agreement with the findings of Koolstra and van Eijden (1997). One must also not forget the unmodeled passive resistance of soft tissue (skin, fat, etc.) surrounding the skeletal structure that affected the activation patterns recorded originally.

Comparing the performance of the two recruitment algorithms, the polynomial recruitment algorithm produced smoother outputs, which suggests that it should be preferred over the min/max criterion that was used before in similar simulations (de Zee et al., 2007). The min/max criterion can result in sudden peaks and discontinuities in the muscle activations, as observed here, if the studied motion involves rapid changes in the accelerations and/or muscle moment arms.

Simulated condylar reaction forces followed closely the reference forces. This further helps verify the inverse dynamics solver, which calculates the constraint reaction forces and the required muscle forces simultaneously. Large forces occur during food crushing/occlusion and those dominate the acceleration and inertial forces of the mandible, which are minimal during that time period. In this phase, quasi-static load balance occurs between all the forces acting on the mandible which include the muscle forces, TMJ reaction forces and external biting/occlusal forces. It is important to note that the transplanted maxilla, in the particular instance of single jaw transplantation, as compared to all other orthognathic surgical procedures, will be of different embryological origin and therefore provide an entire set of forces dissimilar to those experienced by the mandible originally. Therefore accurate modeling of those forces is of crucial importance.

Of note is also the difference between the ratio of working/balancing maximum loads between the swine and human models. Langenbach and Hannam (1999) simulated unilateral chewing and “chopping” motions of human mandible and found that, for a chewing movement, maximum condyle load in the working side is larger than that of the balancing side during occlusal. The opposite was observed in their chopping simulation and in our swine model, in agreement with the reference swine data. It must be noted that the lateral movement of the swine mandible during chewing was much smaller than that of humans, so the swine unilateral chewing could be effectively more similar to human chopping.

The predicted A–P motion of the condyle deviated largely from the reference data in the opening phase and it then closely followed the reference data. This, we hypothesized, could be due to size mismatch between the original and the current model. Scaling the input motion compensated for this error, which supports this assumption.

Understanding the similarities and differences in kinematics and kinetics between human and swine mastication can aid in better large-animal translational FJTT studies, which are warranted to improve outcomes and allow pre-clinical development of

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computer-assisted technologies for such surgeries (Al Rakan et al., in press; Santiago et al., 2014). Among the similarities between swine and human mastication are both the range and profiles of condylar motion (Hannam et al., 2008). During early opening and early closing of the jaw, the balancing side rotates around the hinge-like working side TMJ and therefore has a larger range of A–P motion. The balancing condyle almost returns to its resting position right before the food crush, which is followed by complete return to the rest position by the working side condyle. An anatomical difference between humans and swine that affects the mastication mechanics is the arrangement of the temporalis muscle bundles. In swine, these fibers originate more posteriorly and therefore the line of action of these muscles has a larger horizontal component than the ones in humans. As a result, when these muscles are activated during food crushing, a force component pulls the mandible posteriorly so a counter-balancing force is required to stabilize the jaw. This is likely the source of lateral pterygoid activation, which is usually not seen in human mastication during food crushing (Hannam et al., 2008). However, these differences can be effectively modeled in the software, enabling translation of muscle optimization procedures on swine to humans for FJTT.

While specifically designed for FJTT, studies such as this have implications for a variety of other fields, including craniofacial surgery, oral–maxillofacial surgery, ear–nose–throat (ENT)/head and neck surgery, dentistry and comparative anatomy. For instance, studies of mammalian, reptile, or dinosaur jaw mechanics so far have mostly included forward dynamics simulations with the aim of predicting the maximum bite forces (Bates and Falkingham, 2012; Curtis et al., 2008; Moazen et al., 2008). Inverse dynamics simulations can help better understand the underlying motor control of biting and mastication and, in turn, feeding habits of such animals.

This study provided a first step verification of an inverse dynamics model of swine mastication compared to published data. There were several inevitable sources of discrepancy between the model and the published data of previous forward dynamics simulation. These can be alleviated if data, including EMG signals and incisor trajectories as well as the bony anatomy and muscle parameters, are gathered from the same specimen, which will be part of our future research. Another point of improvement is to add the surface contact model between the lower and upper jaw, as opposed to simple point forces, which will help greatly in planning of transplant surgeries.

Conflict of interest statement

None declared.

Author contributions

All authors were fully involved in the study and preparation of the manuscript. The material within has not been and will not be submitted for publication elsewhere.

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Overcoming Cross-Gender Differences and Challenges in Le Fort–Based, Craniomaxillofacial Transplantation With Enhanced Computer-Assisted Technology

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Background: Sex-specific anthropometrics, skin texture/adnexae mismatch, and social apprehension have prevented cross-gender facial transplantation from evolving. However, the scarce donor pool and extreme waitlist times are currently suboptimal. Our objective was to (1) perform and assess cadaveric facial transplantation for each sex-mismatched scenario using virtual planning with cutting guide fabrication and (2) review the advantages/disadvantages of cross-gender facial transplantation.

Methods: Cross-gender facial transplantation feasibility was evaluated through 2 mock, double-jaw, Le Fort–based cadaveric allotransplants, including *female* donor-to-*male* recipient and *male* donor-to-*female* recipient. *Hybrid* facial-skeletal relationships were investigated using cephalometric measurements, including sellion-nasion-A point and sellion-nasion-B point angles, and lower-anterior-facial-height to total-anterior-facial-height ratio. Donor and recipient cutting guides were designed with virtual planning based on our team's experience in swine dissections and used to optimize the results.

Results: Skeletal proportions and facial-aesthetic harmony of the transplants (n = 2) were found to be equivalent to all reported experimental/clinical sex-matched cases by using custom guides and Mimics technology. Cephalometric measurements relative to Eastman Normal Values are shown.

Conclusions: On the basis of our results, we believe that cross-gender facial transplantation can offer equivalent, anatomical skeletal outcomes to those of sex-matched pairs using preoperative planning and custom guides for execution. Lack of literature discussion of cross-gender facial transplantation highlights the general stigmata encompassing the subject. We hypothesize that concerns over sex-specific anthropometrics, skin texture/adnexae disparity, and increased immunological resistance have prevented full acceptance thus far. Advantages include an increased donor pool with expedited reconstruction, as well as *size-matched* donors.

Key Words: face transplant, craniomaxillofacial, vascularized composite allotransplantation (VCA), sex, cross-gender, intraoperative cutting guide

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Craniomaxillofacial transplantation is a clinical reality that is rapidly gaining acceptance as a suitable alternative to autologous methods for reconstructing massive facial skeletal defects not amenable to standard techniques. As the world continues to gain experience in facial transplantation, indications will broaden as the procedure emerges from its designation as *experimental* to *standard of care* in select patients. Furthermore, advances in immunotherapy, including concurrent donor bone marrow augmentation for immunosuppression minimization,[1] will aid in reducing the requirements for intensive lifelong immunosuppressant regimens. The combination of increased experience, widespread public acceptance, and reduced immunosuppression will further place the limitation of this surgical procedure on donor supply, as seen with solid organ transplantation.

For some programs, a sex-mismatched donor/recipient pair has been listed as a *contraindication* to craniomaxillofacial transplantation.[2] Sex-specific anthropometrics and skin/hair aesthetic mismatch have led to concerns that cross-gender facial transplants will produce inferior hybrid results. However, removing the sex barrier in craniomaxillofacial transplantation would significantly increase the donor pool, providing patients with massive facial skeletal defects with more options for reconstruction. In addition, cross-gender donors could potentially provide appropriately sized donors that may not be available in their sex-matched counterparts.

Donor-to-recipient matching in facial transplantation is confined not only by blood type compatibility and cross-matching but also by phenotypic characteristics and viral mismatch status.[3,4] We believe that skeletal size matching should be weighed heavily when matching donors and recipients, and that strict rules concerning sex matching may be avoided. Furthermore, using virtual surgery pretransplant after donor identification and using intraoperative cutting guides will greatly assist the craniofacial team.

Such considerations have already been demonstrated in upper and lower extremity transplantation, where sex-mismatched pairs are

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accepted.[5,6] Minor concerns over disparities in skin texture and adnexae (ie, facial hair) in the male-to-female face transplant scenario could be addressed postoperatively with electrolysis/laser hair removal. Contour discrepancies related to morphologic differences in skeletal form between men and women could be addressed with bone grafting, alloplastic augmentation, facial skeletal osteotomies, or soft tissue camouflage procedures. In addition, the hormonal milieu (ie, circulating testosterone) of the male recipient receiving a female facial alloflap (and vice versa) may dictate secondary skin/hair characteristics of the vascularized composite alloflap, negating the need for postoperative refinements—as previously described in upper and lower extremity transplant scenarios.[5,6]

The aim of the current study was to investigate facial skeletal harmony and phenotype compatibility after mock cadaveric cross-gender double-jaw, Le Fort–based craniomaxillofacial transplantation. We present a cadaveric study for both possible scenarios including *female-to-male* and *male-to-female*. Emphasis is placed on photograph analysis and hybrid skeletal relationships. Custom cutting guides, by way of 3-dimensional cephalometric imaging, were used to optimize posttransplant skeletal relation. Virtual planning was used and developed by way of experiences learned in our large animal experimental studies. Our laboratory has, to date, conducted 3 cadaveric transplants and 2 live swine Le Fort–based facial transplants, each of which used virtual planning and cutting guides analogous to those described here. Lessons learned from these animal surgeries have been invaluable to our team's progression and has greatly assisted in coordination of resources at the Johns Hopkins University Applied Physics Laboratory (Laurel, MD) and Walter Reed National Military Medical Center (Bethesda, MD).

METHODS

Study Design and Cadaver Procurement

A total of 4 fresh cadaveric heads, 2 women and 2 men, were used in this experimental study to investigate 2 separate scenarios. Selection of female and male donors versus recipients was based on order of possession (Fig. 1A,B). Each dissection was carried out with a consistent double-jaw, Le Fort III–based design, with equivalent recipient defects created bluntly with a rongeur and drill to mimic trauma-related defects indicative of transplant candidacy. Bilateral neurovascular pedicles were dissected completely but not repaired in entirety given the objective of this study. Of note, each cadaver was donated for the sole purpose of medical research and all specimens were obtained, dissected, and managed in accordance with the institutional review board guidelines of The Johns Hopkins University School of Medicine and The Johns Hopkins Hospital.

Virtual Surgical Planning and Execution

In 2011, our laboratory began developing a preclinical, large animal model for the translational investigation of Le Fort–based, craniomaxillofacial allotransplantation in an effort to improve outcomes related to skeletal, dental and aesthetic harmony. For this study, we performed Le Fort III–based facial transplant dissections. This allowed our team the opportunity to use numerous modifications and to identify relevant obstacles related to limited exposure and muscle dissections during live animal surgery, especially because the skeletons are quite similar to humans. As such, the swine's anatomy lends itself well for innovations related to computer-assisted technology for facial transplantation.[7]

For virtual surgical planning, we first perform segmentation and 3-dimensional reconstruction of the recipient and donor CT scans (Mimics 15.01; Materialise, Leuven, Belgium). Virtual osteotomies are then performed within the software to optimize the donor/recipient match and patient-customized cutting guide templates are created (3-matic 7.01; Materialise). These templates are then rapid prototyped via either a stereolithography or fused deposition modeling process.

Recipient Preparation

Massive, central orbitozygomaticomaxillary and mandibular defects spanning from angle-to-angle were created bilaterally in both the female and male recipients (n = 2 transplants), to simulate identical clinical scenarios where autologous methods would be inadequate for reconstruction. Defects included destruction and removal of bilateral orbital floors, nasal bones, maxillae, zygomatic complexes, mandibular symphyses, parasymphyses and bodies, partial soft and complete hard palate. All overlying soft tissue including nose, upper and lower lips, and bilateral cheeks was excised en bloc. Of note, the pterygomasseteric sling was not dissected and left intact, preserving native recipient masticatory function. As the mandible receives partial blood supply from the pterygomasseteric sling, this is an important technical point because the inferior alveolar artery is divided when executing the sagittal split osteotomy resection for recipient preparation. In addition, the inferior alveolar nerve was identified and preserved for ultimate neurorrhaphy.

Donor Alloflap Harvest

For the female and male donor heads (n = 2), double-jaw, Le Fort III–based alloflaps were harvested using handheld osteotomes,

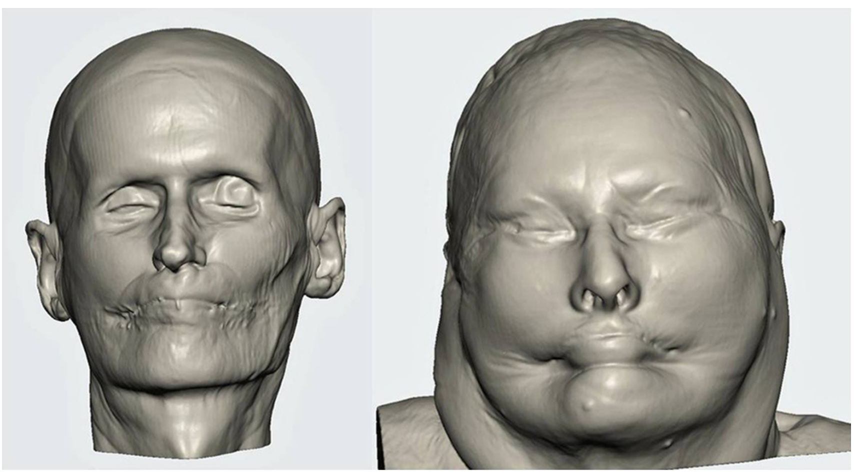

FIGURE 1. Three-dimensional soft tissue reconstructions used in T2MF scenario.

a reciprocating saw, and a fine vibrating reciprocating saw. Both osteocutaneous alloflaps were harvested using a double-jaw, Le Fort III–based design (a craniofacial disjunction), with preservation of the pterygoid plates, incorporating all of the midfacial skeleton, complete anterior mandible with dentition, and overlying soft tissue components necessary for ideal reconstruction. Before transplantation, both scenarios were completed virtually given the sex-specific challenges to allow custom guide fabrication (Fig. 2A–H). Once assimilated, the donor orthognathic double-jaw units were placed into external maxilla-mandibular fixation (MMF) using screw-fixated cutting guides to retain occlusal relationships during the mock transplants (Fig. 3A–D).

Transplantation Protocols

Two separate sex-mismatched allotransplants were successfully completed, with the first being a female *donor*-to-male *recipient* transplant (T1FM), and the second a male *donor*-to-female *recipient* transplant (T2MF). Both transplants were essentially identical, harvesting a Le Fort III–based craniomaxillofacial unit (using a technique previously published by the senior author [CG], including extended zygomatic arches and orbital floors to provide a surplus of osseous support) with bilateral mandibular bodies, and all overlying soft tissue. The osteocutaneous alloflaps were transplanted in MMF to retain donor occlusion, which obviated the need for dental cast models and occlusal splint fabrication previously used by Gordon and colleagues[8,9] in the single-jaw transplant scenario.

Rigid fixation was applied (in order of execution) to the following areas: nasofrontal, zygomaticofrontal, zygomaticotemporal, zygomaticomaxillary, and mandibular angles (Stryker CMF, Kalamazoo, Mich). Soft tissue was closed in usual layered fashion. Once transplantation was complete, MMF was removed and posttransplant maxillofacial CT scans were obtained, including frontal and lateral cephalograms, thin axial slices with sagittal and coronal reformations, and 3-dimensional reconstruction.

Cephalometric Analysis

Cephalometric analyses (Dolphin 3D; Dolphin Imaging, Chatsworth, Calif) were completed for both posttransplant, sex-mismatched, hybrid skeletons (Fig. 4A,B). Emphasis was placed on facial skeletal projection, and facial height and width proportions. However, both donors were transplanted in MMF, and the donor's skeletal relation/occlusion was retained in both scenarios using a double-jaw technique, as expected.[10] Measurements included sellion-nasion-A point (SNA) angle, sellion-nasion-B point (SNB) angle, and lower-anterior-facial-height to total-anterior-facial-height (LAFH/TAFH) ratio (Table 1).

RESULTS

Both cross-gender cadaveric double-jaw, Le Fort III–based allotransplants were successful in achieving acceptable skeletal harmony and appearance consistent with previously reported sex-matched facial transplants (Fig. 5). Operative times of 5.5 and 6.5 hours were equivalent to previously performed cadaveric facial transplantations.[8,9] Of note, transplantation of the donor maxilla and mandible en bloc with presurgically designed cutting guides and extraoral

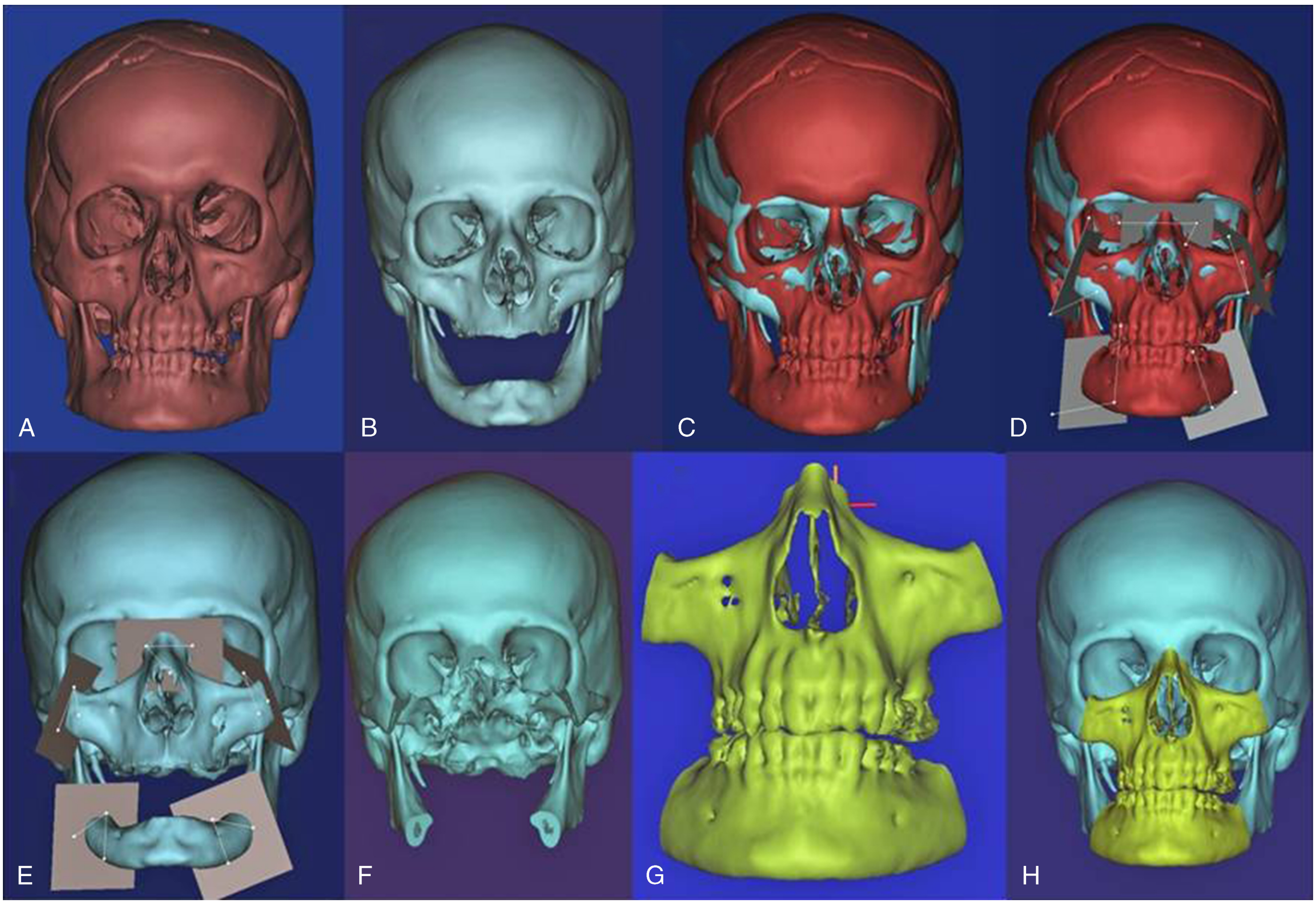

FIGURE 2. Virtual surgical planning in preparation for crossgender facial transplantation.

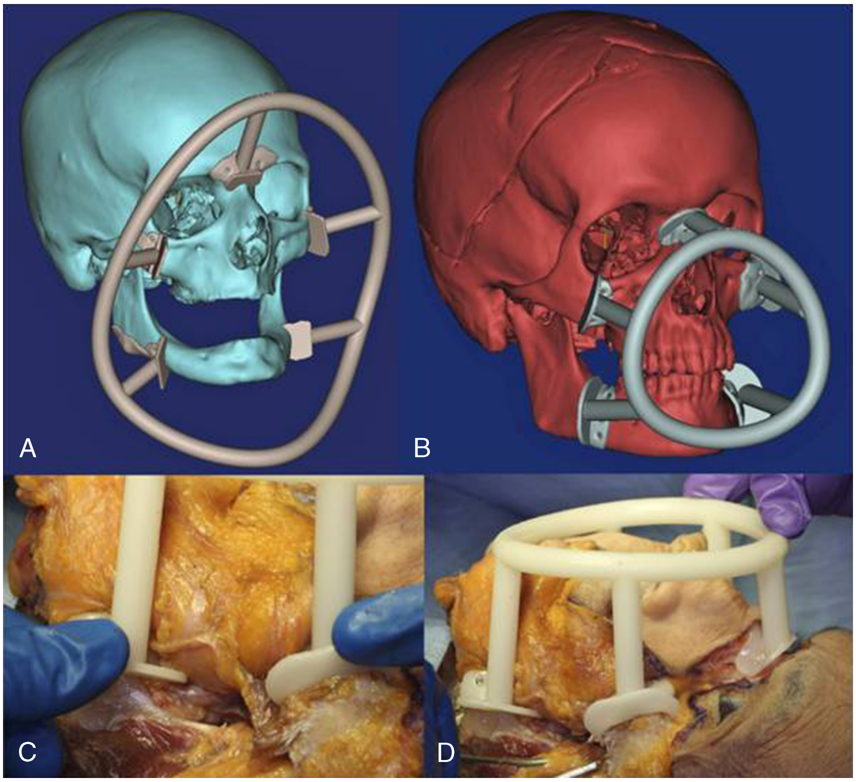

FIGURE 3. Concentric intraoperative cutting guides, showing virtual planning of both recipient (large circle) (A) and donor (small circle) (B), and pretransplant fixation of the small circle on the donor (C and D).

MMF resulted in a mean reduced operative time of 4.5 hours compared to previously published cadaveric transplantations by Gordon et al[8,9] of maxilla alone, which required dental casts and orthognathic splints to improve hybrid occlusion.

Additional time was required for presurgical computer predictions to establish virtual cutting planes on the recipient for skeletal arrangement optimization [average time = 25 min/transplant] and to fabricate computer-manufactured (stereolithography) intraoperative cutting guide/maxillomandibular fixation [average time = 4 h/transplant]. Development of the guides was enhanced by having a simultaneous large animal pre-clinical model involving live swine surgery to practice with and for guide modification based on surgeon feedback (Fig. 6A–E).

In the first mock transplant scenario (ie, T1FM), the male *recipient* retained class I occlusion from the female *donor* as expected. The sagittal position of the *female* maxillomandibular unit was slightly prognathic relative to the *male* cranial base with sellion-nasion-A point (SNA) and sellion-nasion-B point (SNB) angles of 88 and 84 degrees, respectively (Eastman Normal Values: SNA = 81 [3] degrees, SNB = 79 [3] degrees). Facial height proportions were retained with a LAFH/TAFH of 54% (Eastman Normal Value: LAFH/TAFH = 55% [2%]) (Table 1).

For the second transplant, the *male* maxilla achieved proper positioning relative to the *female* cranial base with a SNA angle of 81 degrees. The *male* mandible was slightly retrognathic relative to

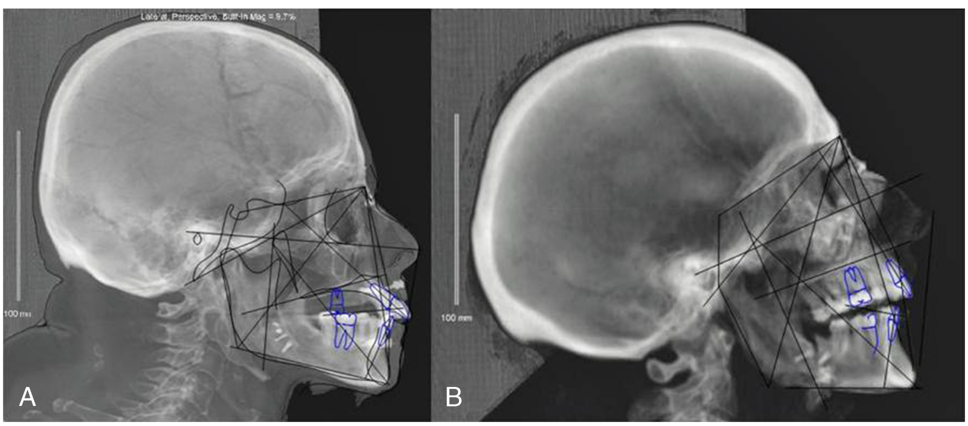

FIGURE 4. Posttransplantation cephalometric tracings of T1FM (A) and T2MF (B).

TABLE 1. Hybrid Skeletal Relationships From Mock Cadaveric Double-Jaw Le Fort–Based Face Transplants

	SNA (SD), degrees	SNB (SD), degrees	LAFH/TAFH (SD), %
Eastman Normal Values	81 (3)	79 (3)	55 (2)
Transplant 1: female to male (T1FM)	88	84	54
Transplant 2: male to female (T2MF)	81	73	55

the *female* cranial base at a SNB angle of 73 degrees. Again, anterior facial height proportions were retained with a LAFH/TAFH ratio of 54% as expected.

DISCUSSION

Facial transplantation is rapidly establishing itself as the ideal method for reconstructing massive soft and hard tissue defects stemming from various etiologies including close-range ballistic, thermal, electrical, and/or trauma-related events. Recipients not only benefit from a restored appearance for reintegration into society but also gain vital functions, including valuable sphincter closure (ie, orbicularis oris and oculi), sense of smell with reestablishment of nasal cavity, taste, facial sensation and movement for expression, eyelid function with globe protection and vision preservation, and oral competence for mastication.

To date, all clinical and experimental facial transplantations described in the literature have been between sex-matched donor-recipient pairs. Our study, for the first time, demonstrates that cross-gender facial transplantation can be accomplished with acceptable hybrid skeletal harmony.

In 1994, Farkas defined normative anthropometric values for a wide range of ethnic groups, including both sexes.[11,12] His work demonstrates that the male craniofacial skeleton has both increased height and width. Yet, skeletal harmony is determined by the relative position and balance of the parts, not by absolute numbers. Moreover, facial height proportions and cranial base-to-facial skeleton angles are largely retained between sexes.[11] This knowledge may raise concerns that crossgender facial transplants would result in a disproportioned hybrid skeleton, as the maxilla-mandibular unit from one sex might not suit the cranial base of the opposite. However, our study exhibits that overall skeletal harmony can be retained after sex-mismatched transplantation by using prefabricated cutting guides and 3-dimensional cephalometric analyses developed in conjunction with our translational swine study. In fact, we believe expanding the donor pool to include transgender donors will further allow for appropriate size matching to achieve correct facial proportions and angles, and assist in minimizing prolonged waitlist times complicated by rare blood type and/or viral seropositive-seronegative matching (Table 2).

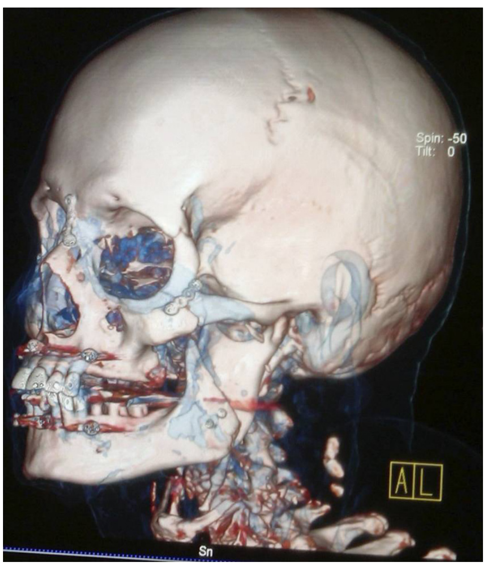

FIGURE 5. Three-dimensional reconstruction of final skeletal harmony in T1FM shown with rigid fixation.

For example, a small male recipient, with preinjury facial height and width on the lower end of normal for men, would be matched to a suitable donor more expeditiously when women are included, who on average would have similar facial height and width, yielding appropriate proportions. This would be similar to situations already described in upper extremity and lower extremity VCA.[5,6] In addition, the cadavers used in our study were selected based on order of possession, and satisfactory facial proportions were still achieved with the use of computer-generated virtual surgical evaluation and 2-team planning. In contrast, transgender facial transplantation would only be undertaken clinically if the donor-recipient pair was ideally size matched, greatly improving outcomes compared to our experimental cadaver study.

The use of advanced computer planning and execution technology offers an enhanced ability to achieve precise outcomes and identify when a donor is a poor match for the recipient. We were able to obtain excellent donor to recipient harmony even across sexes by using virtual surgical planning. Having a translational model in swine is also valuable for simultaneous innovation. Furthermore, the use of the virtual environment allows extensive experimentation to find the optimal alloflap design and inset to produce the best result. Importantly, potential concerns that some cross-gender pairs would be too disharmonious—for example, a male might have a small enough face but highly masculine shape to the mandible that would create a poor aesthetic result—are mitigated by the fact that a donor-recipient pair yielding a poor result is readily identified in the computer planning phase before a commitment to transplantation is made.

As the facial transplantation pool of potential donors and recipients begins to increase, the ability of imaging analysis software (eg, the Dolphin 3D package) to quantitate and store important cephalometric values offers exciting potential. Once hard factors such as immunologic compatibility have been matched, the remaining potential recipients can be identified and ranked based on their degree of anthropometric similarity. A key aspect of this work lies in providing data to support development of such algorithms, which we believe should emphasize similar skeletal structures over factors such as sex.

Skin texture and adnexae disparities, especially facial hair, create a second point of reluctance to include sex-mismatched donors for craniomaxillofacial transplantation. Interestingly, a *female*-to-*male* bilateral lower extremity vascularized composite allotransplant case was recently presented.[6] It was reported and demonstrated that the transplanted female lower extremity grew similar hair to that of the recipient's legs in context of the male hormonal milieu. Also, there was no report of psychological inhibition by either the recipient and/or donor family. Such outcomes have also been anecdotally

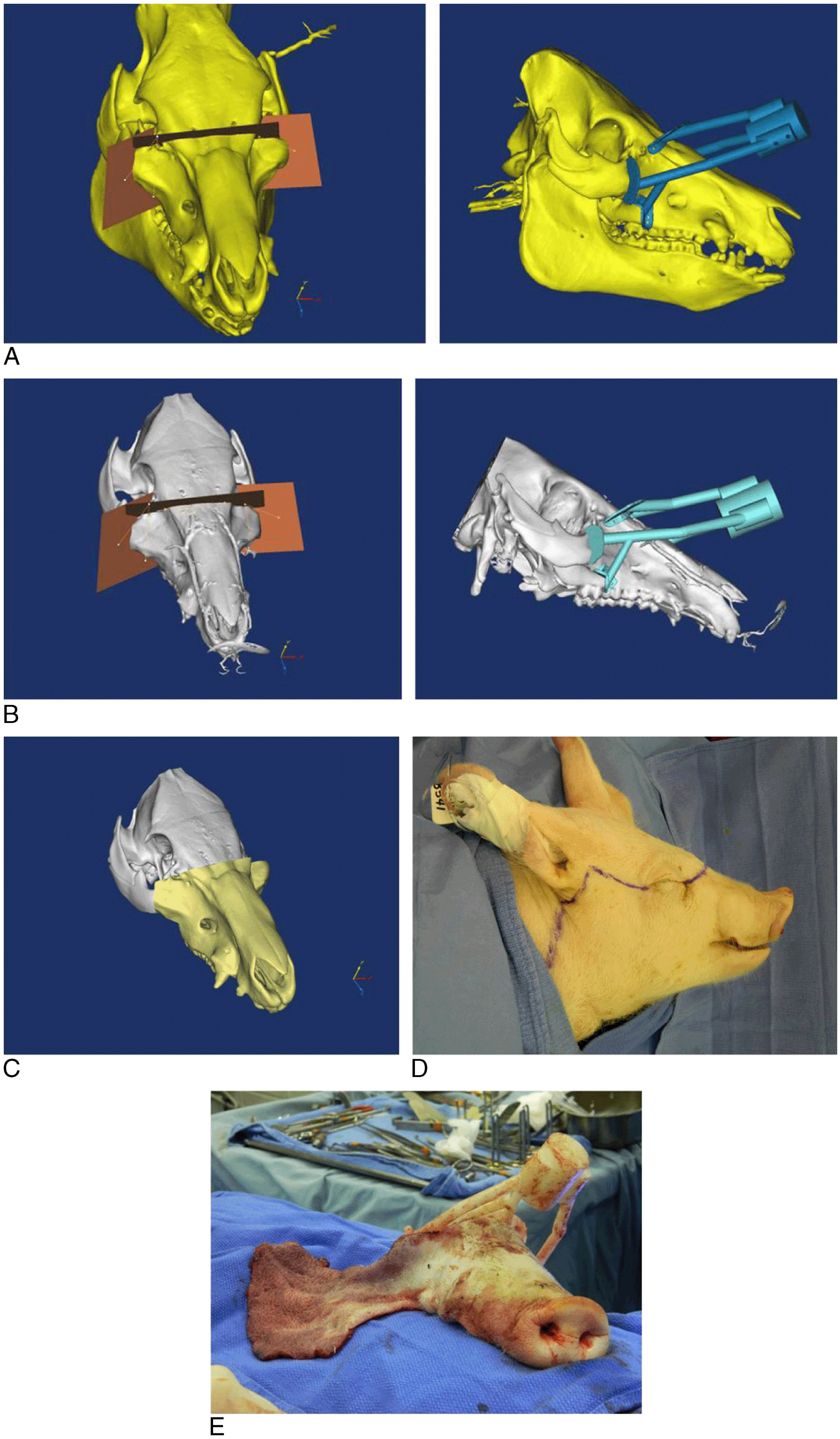

FIGURE 6. Images from translational swine surgery depicting (A) preoperative virtual planning and cutting guide images on larger donor skeleton for Le Fort III–based facial transplantation, (B) preoperative virtual planning and cutting guide images on smaller recipient skeleton, (C) predicted ''hybrid'' transplant result, (D) incision design in donor for transplant, and (E) final cutting guide position with dissected osteocutaneous maxillofacial alloflap.

TABLE 2. Advantages and Disadvantages of Crossgender, Le Fort–Based Facial Transplantation

Advantages	Disadvantages
Increased donor pool (ie, nearly doubling in size)	Skin texture/adnexae mismatch (ie, facial hair)
Size-matched donor-recipient pairs (ie, based on buttress height, width, and projection rather than sex)	Sex-specific anthropometrics
Decreased time on waiting list (ie, may save months to years for some patients)	Potential for increased rate and severity of immunological rejection based on sex mismatch
Allows teams to be more selective (ie, CMV donor/recipient seronegative matching)	Psychological obstacles

reported in transgender upper extremity transplantation patients, with the first being performed in Poland.[5]

Although not specifically addressed by our study, we believe that concerns over skin texture and adnexae mismatch in transgender *female-to-male* facial transplantation will be put to rest due to recipient hormonal influences on the alloflap. Furthermore, facial hair mismatch in the reverse scenario could be specifically addressed by laser hair removal and/or makeup if there were small discrepancies despite the influence of recipient hormones (ie, circulating estrogen and lack of testosterone). Although this will be more challenging, as many facial transplant recipients undergo revisional surgery, these patients could very well undergo skeletal manipulation with alloplastic augmentation and/or skeletal reduction (ie, forehead, maxilla, or mandible), if necessary for correcting improper feminization and/or masculinization.

Interestingly, earlier graft loss in donor-recipient sex-mismatched pairs is well documented in solid organ transplantation.[13] Male recipients of female kidneys have worse short-term and long-term graft survival compared to male-to-male pairs and female recipients of donors of either sex. Causes of these survival discrepancies are largely unknown, and explanations include nephron underdosing (ie, size mismatch), immunological barriers, hormonal influences on the endothelium, and sex differences in susceptibility to ischemia/reperfusion. One study reports worse renal allograft survival in female recipients of male kidneys; postulating that maternal presensitization may play a role.[14] Furthermore, there is a higher rate of rejection episodes requiring treatment after *female-to-male* kidney transplantation, speaking to possible immunological causes of graft failure. Similar results have been seen in heart and liver transplantation, with shorter graft survival in male recipients of female donors.[13] However, these results are not uniform and have been contradicted by reports of equivalent outcomes regardless of sex mismatch.[15] Also, the rate of rejection episodes requiring treatment in heart and liver transplantation is equivalent across all sex pairings. However, causes of differential allograft survival in solid organ transplantation are not clearly established, which may be of great interest to VCA researchers. Heart, liver, and kidney transplantation must overcome not only immunological barriers but also physiological obstacles as well. Potential immunological barriers between sexes need to be taken into consideration, but VCA bypasses issues with differential sex physiology and eliminates most of the hypothesized causes of worse allograft survival after sex-mismatched solid organ transplantation. Alloflap survival after upper and lower extremity transgender transplantation serves as a better predictor for crossgender craniomaxillofacial allotransplantation as compared to solid organ outcomes.

Limitations to this study include its small sample size and the inability to directly address some of the potential issues raised (ie, facial hair growth and sex-specific alloflap survival). However, the aim of the investigation was to analyze appearance and facial skeletal harmony after cadaveric crossgender facial transplantation to address outcome feasibility. This study provides a foundation for further investigation, demonstrating that the building blocks of craniomaxillofacial transplantation, the facial skeleton, are able to achieve proper proportions in sex-mismatched pairs (Fig. 7A,B).

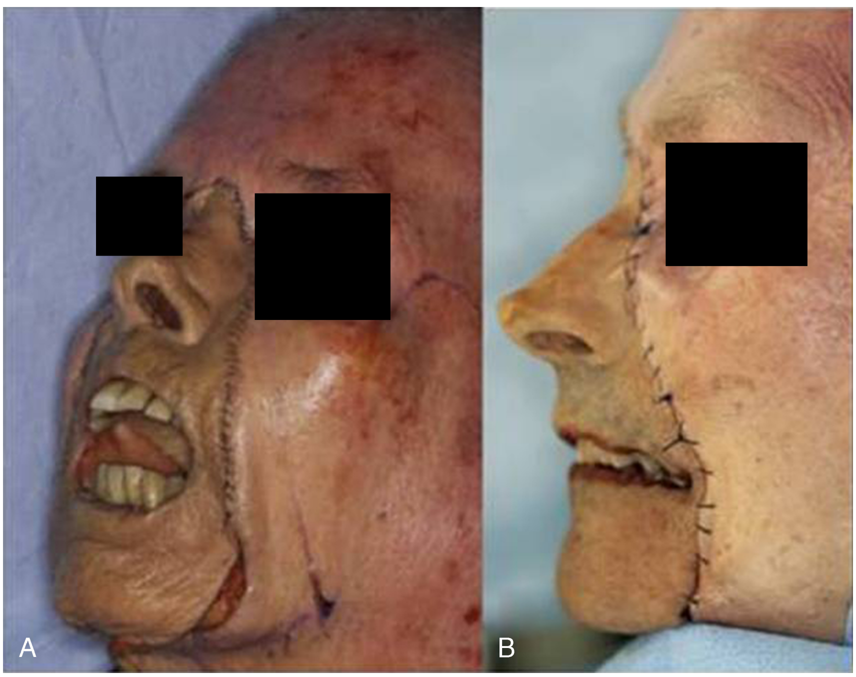

FIGURE 7. Final views of T1FM (A) and T2MF (B).

CONCLUSIONS

Donor supply is limited for craniomaxillofacial allotransplantation, sometimes requiring candidates to wait numerous years before acceptable match. Expanding the donor pool to include sex-mismatched pairs may decrease wait time to reconstruction and allow for skeletal size and viral serology matching. Hybrid facial skeletal harmony can be achieved between sex-mismatched pairs. Presurgical computer predictions and intraoperative cutting guides aid in achieving desired skeletal proportions. Translational large animal models investigating orthotopic, Le Fort–based, maxillofacial transplantation assist developments in enhanced computer-assisted technology and cutting guide modification. Further investigation is warranted to address the feasibility of crossgender facial transplantation for hair growth, psychological impact, and immunological rejection.

ACKNOWLEDGMENTS

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Establishing Cephalometric Landmarks for the Translational Study of Le Fort–Based Facial Transplantation in Swine: Enhanced Applications Using Computer-Assisted Surgery and Custom Cutting Guides

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Background: Le Fort–based, maxillofacial allotransplantation is a reconstructive alternative gaining clinical acceptance. However, the vast majority of single-jaw transplant recipients demonstrate less-than-ideal skeletal and dental relationships, with suboptimal aesthetic harmony. The purpose of this study was to investigate reproducible cephalometric landmarks in a large-animal model, where refinement of computer-assisted planning, intraoperative navigational guidance, translational bone osteotomies, and comparative surgical techniques could be performed.

Methods: Cephalometric landmarks that could be translated into the human craniomaxillofacial skeleton, and that would remain reliable following maxillofacial osteotomies with midfacial alloflap inset, were sought on six miniature swine. Le Fort I– and Le Fort III–based alloflaps were harvested in swine with osteotomies, and all alloflaps were either autoreplanted or transplanted. Cephalometric analyses were performed on lateral cephalograms preoperatively and postoperatively. Critical cephalometric data sets were identified with the assistance of surgical planning and virtual prediction software and evaluated for reliability and translational predictability.

Results: Several pertinent landmarks and human analogues were identified, including pronasale, zygion, parietale, gonion, gnathion, lower incisor base, and alveolare. Parietale-pronasale-alveolare and parietale-pronasale–lower incisor base were found to be reliable correlates of sellion-nasion–A point angle and sellion-nasion–B point angle measurements in humans, respectively.

Conclusions: There is a set of reliable cephalometric landmarks and measurement angles pertinent for use within a translational large-animal model. These craniomaxillofacial landmarks will enable development of novel navigational software technology, improve cutting guide designs, and facilitate exploration of new avenues for investigation and collaboration. (*Plast. Reconstr. Surg.* 133: 1138, 2014.)

Le Fort–based, single-jaw maxillofacial allotransplantation is a novel reconstructive alternative, with only nine operations being performed to date.[1–3] Facial skeletal allotransplantation allows for unprecedented restoration of skeletal form, in addition to sensory, functional, and soft-tissue midface reconstruction.[4] Despite these advances, many transplant recipients have been left with suboptimal dentofacial deformities such as skeletal malalignment, malocclusion, retrognathia, anterior open bite, and aesthetic disharmony.[5]

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Until recently, the concept of "hybrid occlusion" had not been proposed; the term "hybrid occlusion" (first described by our team) represents the posttransplant relation of two human jaws of varying anthropometrics (i.e., a native jaw and an allograft jaw). This terminology was introduced following a cadaver study investigating Le Fort–based, craniomaxillofacial allotransplantation.[1] Findings have suggested that preoperative planning using cephalometric analysis of donor and recipient may lead to improved postoperative skeletal relation, facial harmony, and optimized occlusion.[1,2,4,5]

The use of swine as a reliable model for craniofacial surgery has been well described.[6–9] Given the previously described challenges, a suitable large-animal model on which perioperative techniques can be practiced, reproduced, and refined is an essential investigative tool. Furthermore, with recent advances in computer-assisted planning for skeletal surgery, such a model would allow investigators the rare opportunity to use computer-enhanced technology and design custom surgical guides.[10,11]

Although small-animal models and human cadaver studies have added significantly to the literature on craniomaxillofacial allotransplantation, they are not without their limitations. Small-animal models, such as those described by Ulusal et al. in rats, are highly limited in their ability to be used to study translational osteotomies and to develop new techniques and/or technologies because of their facial skeletal size and anatomical limitations.[13] Similarly, human cadaver studies, although the most analogous model for clinical practice and used by several groups to successfully plan operations and optimize skeletal fixation, are limited by the lack of a suitable live-model surgery analogue, biomechanical obstacles associated with one's masticatory muscles resulting from the cadaver's rigor mortis, and limited jaw mobility.[1,2,5,14,15] Cadavers also have limited potential for assessment of the safety and clinical outcomes of new innovations following transplantation and are therefore inadequate for our study's aims.[1]

The purpose of this study was to develop a swine orthotopic face transplant model. Our group hypothesized that it would be possible to identify and establish a set of reproducible landmarks for the preclinical investigation of skeletal harmony and hybrid occlusion. Our specific aims were to identify translational cephalometric landmarks in swine that were analogous to human landmarks to allow for data collection and validation. A secondary aim was to develop a novel computer-assisted planning and execution system for adaption to both large-animal and human preoperative surgical planning and intraoperative surgical navigation.[12] To our knowledge, this is the first study to implement computer-assisted cephalometric analysis in swine.

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MATERIALS AND METHODS

We sought to identify skeletal landmarks that could be translated to the human craniofacial skeleton and vice versa. Three main sets of landmarks were proposed: (1) an angular set to the cranium, (2) a linear set for the maxillomandibular relationship, and (3) a linear set for the sagittal maxillomandibular relationship along the occlusal plane. Craniofacial landmarks that could be readily translated to the human facial skeleton, would remain reliable following maxillofacial osteotomies and midfacial alloflap inset, and were within or outside the lines of planned osteotomies were to be identified on six miniature swine skulls of varying age, sex, and size (Figs. 1 through 3). Anthropometrics of swine and human cadaver skulls were initially compared based on prior work by our group, and homologous craniofacial landmarks were chosen as candidates[1,6,7] (Table 1).

Following landmark identification, cephalometric analyses were performed on native pig craniums and mandibles using the Dolphin Imaging Plus program (Dolphin Imaging, Chatsworth, Calif.) (Fig. 3, *below*, and Fig. 4). Two swine subsequently underwent Le Fort III–based midfacial alloflap harvest followed by autotransplantation and rigid fixation. Anteroposterior and lateral cephalometric analyses were performed on all autotransplanted swine postoperatively. In parallel, we concentrated on confirming adequate perfusion to our alloflap design for the purpose of translational study with near-infrared laser angiography

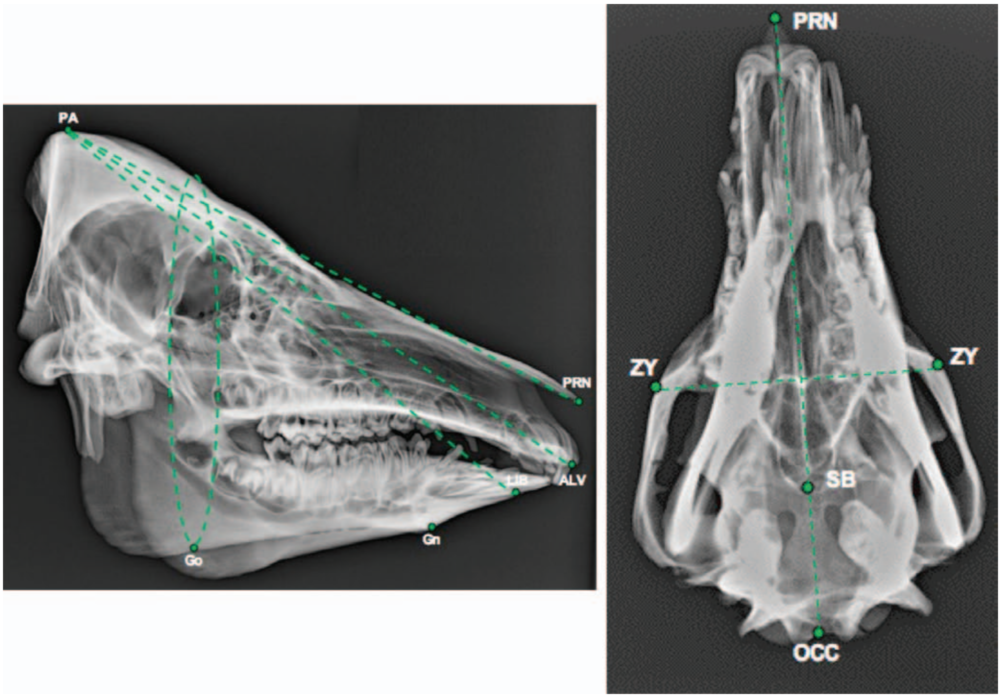

Fig. 1. Preliminary results validating cephalometric (hard tissue) data for translational studies in swine. *PA*, parietale; *PRN*, pronasale; *ALV*, alveolare; *LIB*, lower incisor base; *GN*, gnathion; *GO*, gonion; *ZY*, zygion; *SB*, skull base; *OCC*, occipitale.

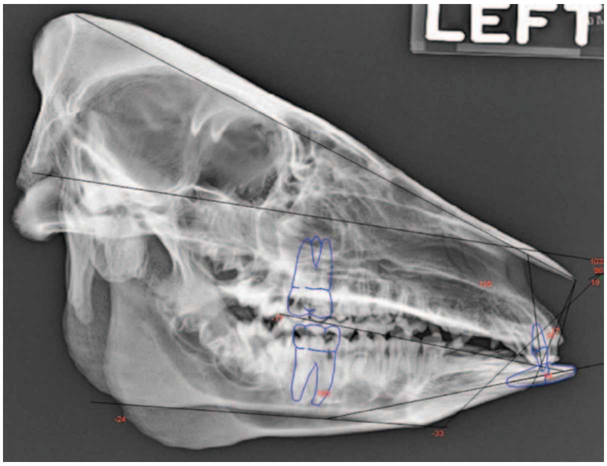

Fig. 2. Lateral cephalogram of a large native swine skull with cephalometric markings and outlines of the first molars.

(Figs. 5 and 6). Once vascularity was confirmed, our team moved forward with allotransplantation in the setting of custom surgical osteotomy guides and used virtual planning to offset the challenge of large size-mismatch discrepancies. To achieve excellent orthognathic profiles, dental alignment, and corresponding aesthetic harmony in both autotransplants and allotransplants, we investigated numerous designs for cutting guide fabrication and modified them with each operation performed (Fig. 7, *above, left*, and *right*). This was done in collaboration with the 3D Medical Applications Center at Walter Reed National Military Medical Center (Bethesda, Md.).

Our team was able to design navigational hardware and software based on our collaborator's previously published experience with navigational technology in orthopedic surgery.[11,12] Development of our large-animal model provided a preclinical platform for the development of a computer-assisted planning and execution (CAPE) system, applicable to all types of complex craniomaxillofacial surgery, including facial allotransplantation. Our goal was to combine preoperative planning and intraoperative surgical navigation into one system that enabled a high degree of precision and reproducibility in craniofacial surgery (Fig. 7, *below, left*, and Fig. 8). Our collaboration with the Johns Hopkins University Applied Physics laboratory was critical for this portion of our project.

After refining the autotransplantation technique, we sought to determine whether the postoperative maxillomandibular relationship could be enhanced with the aid of computer-assisted preoperative planning and live-intraoperative surgical navigation in coordination with custom surgical guides. Donors and recipients were obtained and purposely chosen based on a large size-mismatch

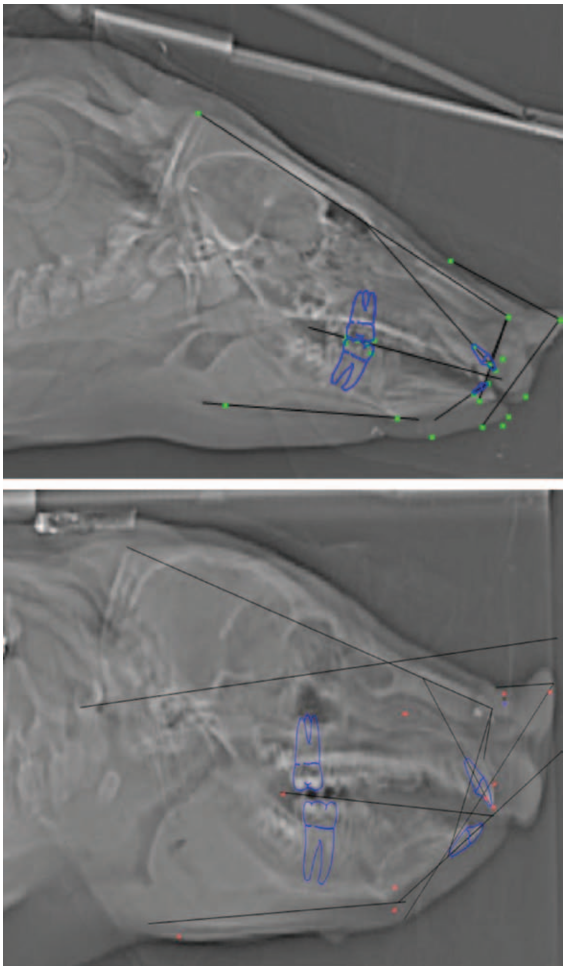

Fig. 3. (*Above*) Preoperative cephalometric analysis of native donor swine mandible and maxilla depicting parietale-pronasale and the occlusal plane. Outline tracings of the first molar and the central incisor are shown. (*Below*) Preoperative cephalometric analysis of native recipient swine mandible and maxilla. Outline tracings of the first molar and the central incisor are shown.

skeletal discrepancy in an effort to challenge the aforementioned innovations. Both size-mismatched transplant procedures consisted of transplanting a larger maxillofacial alloflap onto a smaller recipient. Two live orthotopic Le Fort–I based allotransplantations were performed with the use of a computer-assisted planning and execution (CAPE) system. The virtual planning for these operations was performed by means of three-dimensional computed tomographic scan reconstruction files of the recipient and donor. Virtual osteotomies were then performed using MIMICS software to optimize the donor/recipient match (Fig. 9). Custom cutting guide templates were designed and navigational registration elements were added (Freeform Plus; 3D Systems, Rock Hill, S.C.). The surgical guides were manufactured by means of stereolithography or fused deposition modeling additive manufacturing technology, as described previously by our team (Fig. 7, *right*).[12] Cephalometric analysis was performed postoperatively using Dolphin 3D to evaluate the facial skeletal maxillary-mandibular relationship, and to identify whether optimal "hybrid occlusion" was obtained through the use of this preliminary technology.

RESULTS

Several cephalometric landmarks were identified and found to be conserved in translational fashion from swine to humans and vice versa. After analysis, we identified various pertinent points, including pronasale, zygion, parietale, gonion, gnathion, lower incisor base, and alveolare. Each of these landmarks remained consistent throughout the study (Table 1).

These landmarks were then incorporated into a comprehensive system of cephalometric data sets, and the most reproducibly identifiable points were used to compare all native and postoperative swine skulls (Tables 2 and 3). Refinement of our perioperative procedures during this time included tracheostomy placement with a custom-ordered elongated appliance and wire-reinforced tubing, transitioning over from an esophagostomy to percutaneous gastrostomy

Table 1. Cephalometric Landmarks Used for Preoperative and Postoperative Analysis in the Swine Skull and Their Analogues in the Human Skull

Swine Cephalometric Landmark	Definition in Swine	Human Analogue
GO	Gonion: a point midway between points defining angles of the mandible	Gonion
GN	Gnathion: most convex point located at the symphysis of the mandible	Menton
ALV	Alveolare: midline of alveolar process of the upper jaw, at the incisor-alveolar junction	A point
LIB	Lower incisor base: midline of anterior border of alveolar process of mandible at the incisor-alveolar junction	B point
PA	Parietale: most superior aspect of skull in the midline, (formed by nuchal crest of occipital bone and parietal bone)	Sella (S)
PRN	PRN (pronasale): bony landmark representing anterior limit of nasal bone	Rhinion
ZY	Zygion: most lateral point of malar bone	Zygion

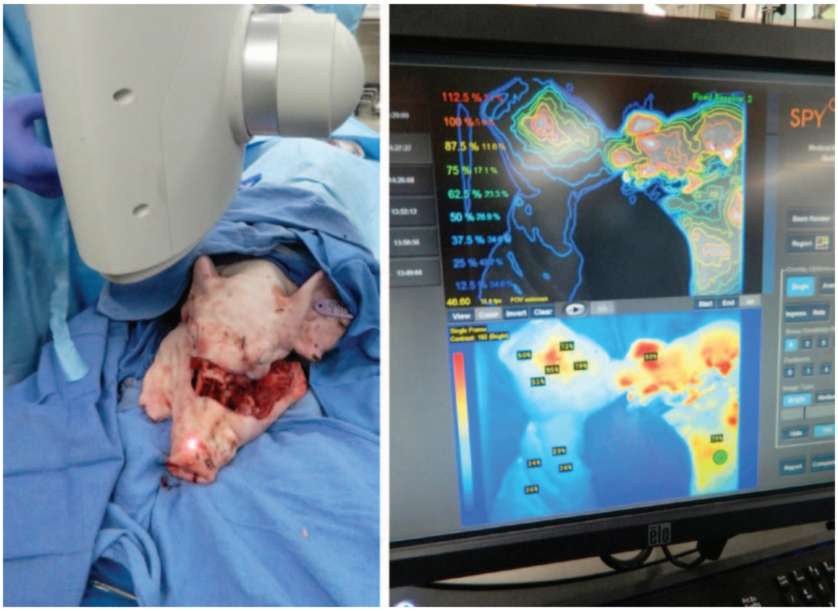

Fig. 4. Intraoperative view and near-infrared laser imaging assessment of swine following Le Fort–based osteotomies with preservation of right vascular pedicle and viable snout perfusion. The swine's left vascular pedicle has been divided as demonstrated in both images.

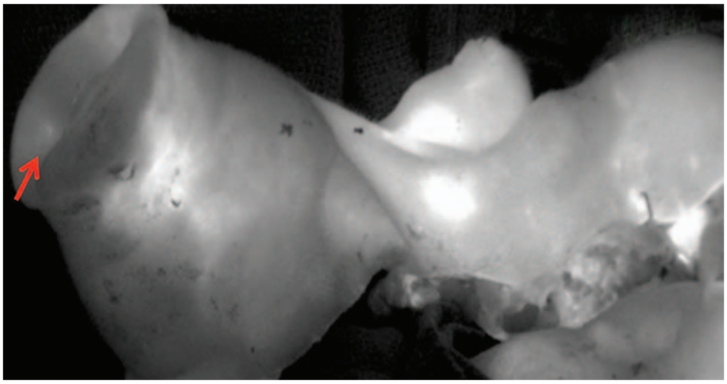

Fig. 5. Near-infrared laser angiography demonstrates acceptable blood perfusion to the tip of the snout (*red arrow*) following a Le Fort–based, maxillofacial flap dissection. The alloflap is completely free from all surrounding facial skeletal structures, with perfusion based solely on bilateral pedicles, which is directly translational to humans.

tube, and adjusting from cervical to femoral placement of a Hickman tunneled catheter.

Both Le Fort III–based autoreplantations and Le Fort I–based allotransplantations were successful in achieving acceptable postoperative skeletal relationships when compared to reference values of native pig skulls. Previous Le Fort–based human cadaveric transplant studies used a system of cephalometric measurements to determine facial skeletal relation (Fig. 10).[1,2] The measurements in those studies evaluated sellion-nasion–A point angle, sellion-nasion–B point angle, and lower anterior facial height–to–total anterior facial height ratio. By using the swine correlates to human cephalometric landmarks in Table 1 as a reference, we chose to use the angle of parietale-pronasale-alveolare as a corollary to the sellion-nasion–A point measurement in humans. We chose to measure the angle of parietale-pronasale–lower incisor base as a corollary to the sellion-nasion–B point measurement in humans and alveolare-pronasale–lower incisor base as a corollary to the sellion-nasion–A point angle in human cephalometric Steiner analysis.

Fig. 6. Planned markings include incisions (*solid lines*) and maxillary osteotomy (*dotted lines*) for Le Fort I facial alloflap harvest.

This study did not evaluate facial height in the swine skull as had been done in prior human cadaver studies because of morphologic differences between swine and human skulls (swine having more prominent premaxillae than humans) (Figs. 11 and 12).[10] We chose instead to evaluate occlusal angle to parietale-pronasale (Fig. 3, *below*), as these values in native skulls tended to fall within a close range of each other (Table 3).

Native Cephalometric Values

A total of eight native skulls were evaluated with cephalometry preoperatively, and four hybrid swine skulls were evaluated postoperatively ($n = 4$ operations). The range of normal values for parietale-pronasale-alveolare (human sellion-nasion–A point correlate) for native swine skulls was 97.0 to 110.6 degrees. The mean parietale-pronasale-alveolare value of native swine skulls was 104.0 degrees. The range of normal values for parietale-pronasale–lower incisor base (human sellion-nasion–B point correlate) for native (nonoperated) swine skulls was 81.1 to 94.7 degrees. The mean parietale-pronasale–lower incisor base value of native

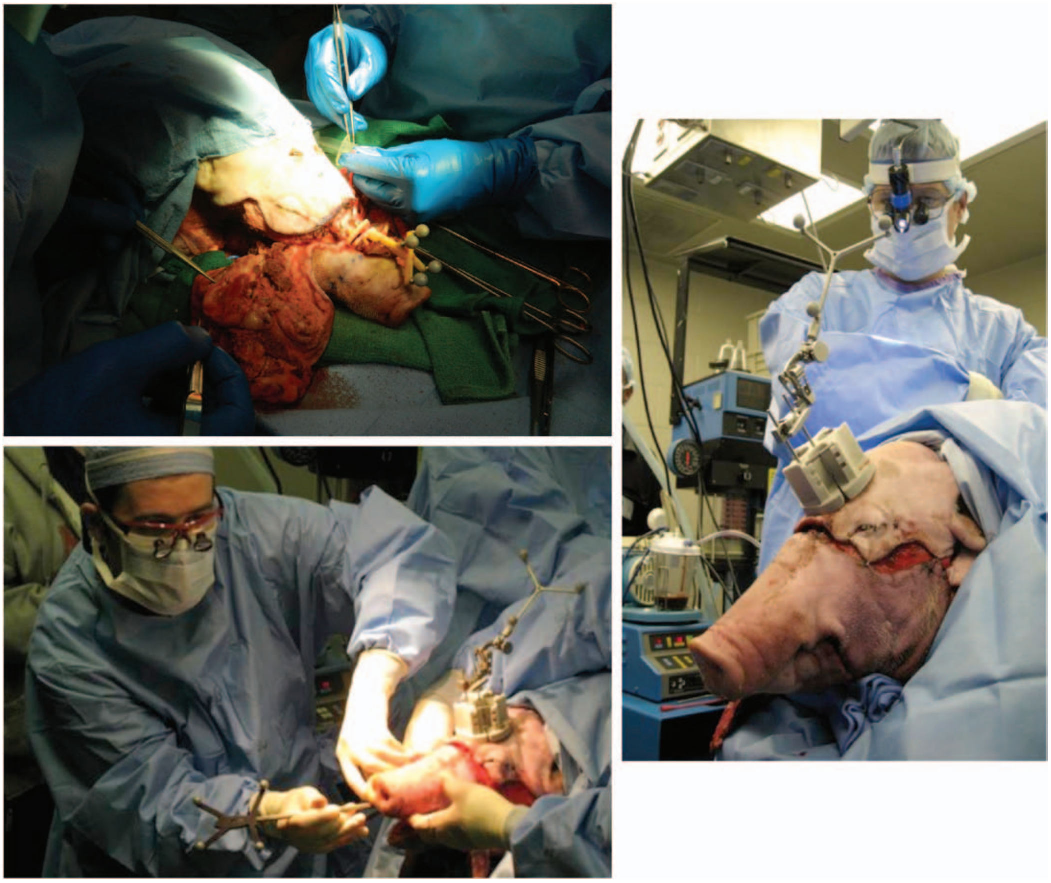

Fig. 7. (*Above, left*) Intraoperative facial alloflap harvest. Real-time surgical navigation hardware with tracking spheres and cutting guide attached to a bony component of the flap. (*Right*) Navigational hardware assembly designed by the Applied Physics Laboratory for three-dimensional registration of the cranium. (*Below, left*) Navigational instrument used for three-dimensional registration of the maxillofacial alloflap.

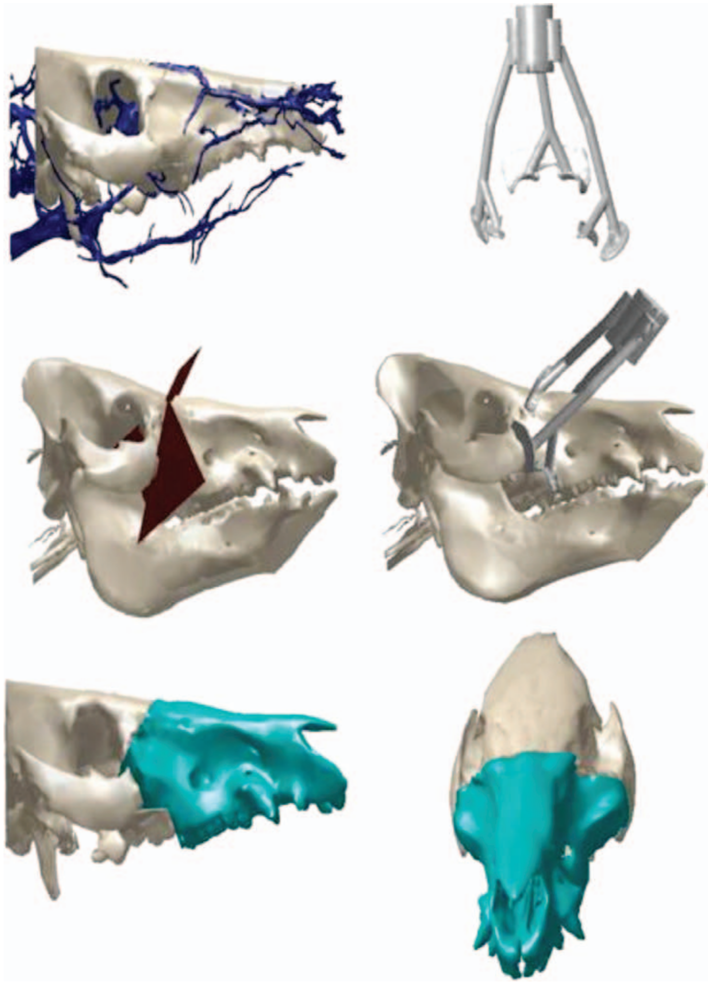

Fig. 8. Virtual planning of the transplants was performed by means of three-dimensional computed tomographic scan reconstruction files of donor and recipient. Virtual osteotomies were then performed using MIMICS software (Materialise, Leuven, Belgium) to optimize the donor/recipient match in collaboration with the 3D Medical Applications Center at Walter Reed National Military Medical Center.

swine skulls was 88.3 degrees. The range of normal values for alveolare-pronasale–lower incisor base (human A point–nasion–B point correlate) for native swine skulls was 3.1 to 25.1 degrees. The mean alveolare-pronasale–lower incisor base value of native swine skulls was 14.5 degrees. The range of normal values for the angle of parietale-pronasale to occlusal plane for native swine skulls was −9.6 to −16.6 degrees. The mean angle of parietale-pronasale to occlusal plane value in native swine skulls was −12.5 degrees.

Postoperative Cephalometric Values

Autotransplant Scenarios

The first and second Le Fort III autotransplant scenarios resulted in retained class I occlusion (defined as the mesiobuccal cusp of the swine's maxillary first molar aligned over the buccal groove of the mandibular first molar) (Fig. 13, *above*). Postoperatively, the mean change in parietale-pronasale-alveolare angle was 2.25 degrees, the mean change in parietale-pronasale–lower incisor base was 0.65 degree, and alveolare-pronasale–lower incisor base change was minimal at −1.75 degrees. The angle of parietale-pronasale to the occlusal plane also remained relatively stable, with a mean change of only 1.4 degrees postoperatively.

Size-Mismatched Allotransplants

Following the completion of two autotransplants and simultaneous validation of reproducible

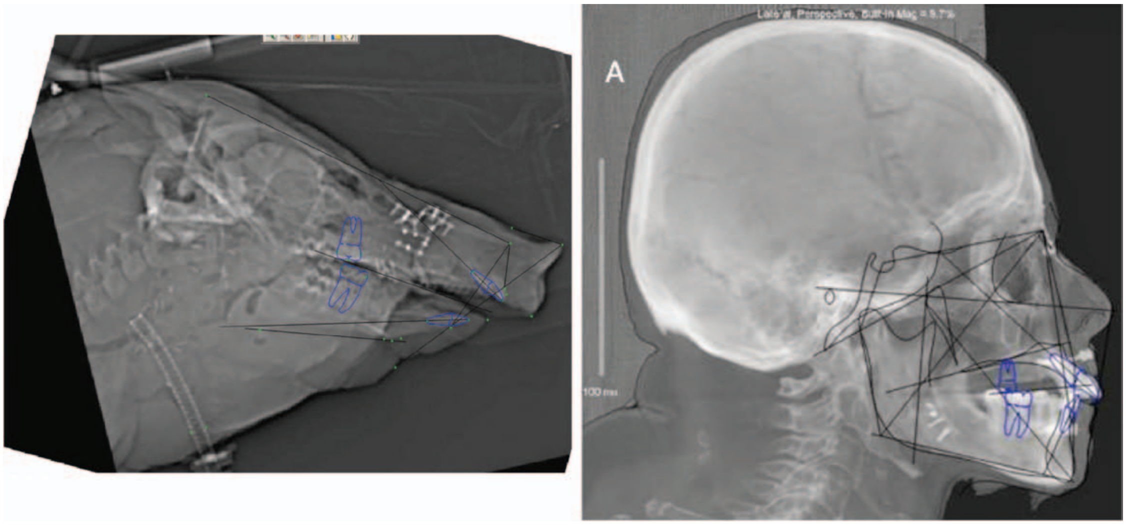

Fig. 9. Postoperative result. Lateral cephalograms showing translation of surgical techniques of Le Fort–based facial allotransplantation from swine to humans.

Table 2. Cephalometric Measurements*

Swine	OCC-PRN	ZY-ZY	PA-PRN	GO-GN	GO-LIB	PA-ALV	PA-ALV-LIB (degrees)	Overbite	Overjet	LIB-ALV
Large native skull	118.4	85.6	191.6	110.6	4.8	198.6	4.8	3	−10	9.5
Small native skull	103.2	84.8	182.3	82.5	6.33	190.5	6.33	3.2	3.2	20.1
First LF III replantation										
Preoperatively	142.6	95.7	253.5	150.8	4.85	260.5	4.85	3	5.1	24.7
Postoperatively	143.2	96.2	259.2	150.8	4.85	265.3	4.75	3.8	4.6	25.1
Second LF III replantation										
Preoperatively	141.6	96.9	184.8	75.8	112.2	197.1	4.4	−8	−12	1
Postoperatively	142.9	95	198.2	75.8	112.2	207.6	4.8	2	5	18

OCC, occipitale; PRN, pronasale; ZY, zygion; PA, parietale; GO, gonion; GN, gnathion; LIB, lower incisor base; ALV, alveolare; LF, Le Fort.
*Data are presented in millimeters.

Table 3. Cephalometric Measurements

Swine	PA-PRN-ALV (degrees)	PA-PRN-LIB (degrees)	ALV-PRN-LIB (degrees)	Occlusal Angle to PA-PRN (degrees)
Small native skull	104.6	94.7	9.9	−16.1
Large native skull	97.0	93.9	3.1	−16.6
Autotransplant 1 (preoperative)	106.7	87.9	18.9	−9.3
Autotransplant 1 (postoperative)	108.6	87.8	20.8	−11.7
Autotransplant 2 (preoperatively)	104.4	92.8	11.6	−9.6
Autotransplant 2 (postoperative)	107.0	94.0	12.9	−10.0
Allotransplant 1 donor (20 kg)	101.2	83.8	17.5	−13.9
Allotransplant 1 recipient (15 kg)	110.6	81.1	29.6.0	−12.1
Allotransplant 1 postoperative recipient	111.9	71.4	40.4	−14.1
Allotransplant 2 donor (23.1 kg)	99.0	89.0	9.0	−11.8
Allotransplant 2 recipient (20.0 kg)	108.6	83.5	25.1	−10.5
Allotransplant postoperative recipient	109.2	80.7	28.5	−8.5

PA, parietale; PRN, pronasale; ALV, alveolare; LIB, lower incisor base.

postoperative cephalometric data points in swine, we proceeded with performing significant size-mismatched allotransplantations. The difference in weight between donor and recipient for the first and second transplant scenarios was 5 and 3.1 kg, respectively. The difference in preoperative and postoperative values for parietale-pronasale-alveolare (analogous to human cephalometric sellion-nasion–A point) was 1.3 degrees in allotransplant 1 and 0.6 degree in allotransplant 2. The difference in preoperative and postoperative values for parietale-pronasale–lower incisor base (analogous

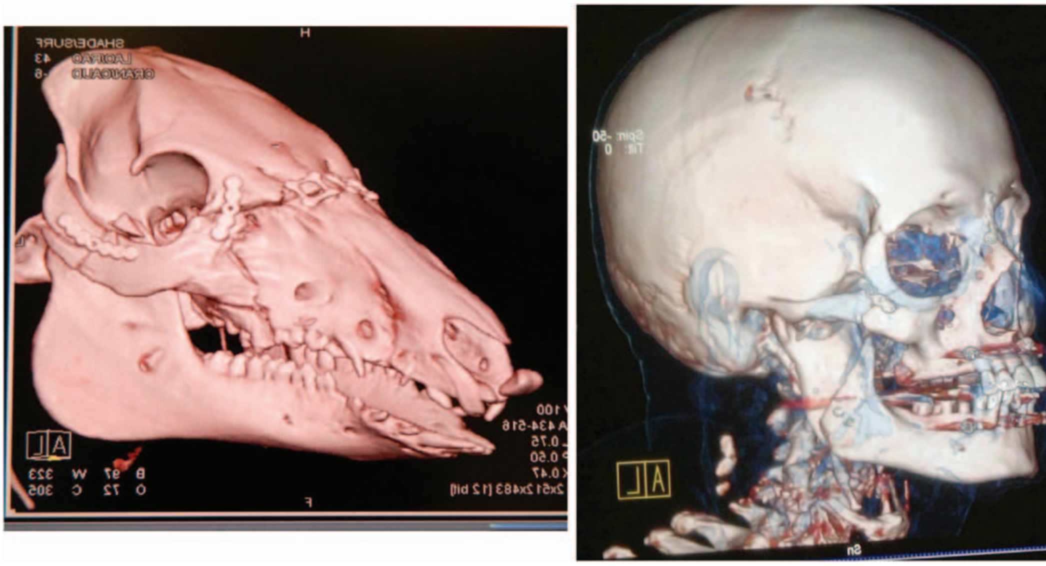

Fig. 10. Postoperative result. Three-dimensional computed tomographic reconstructions showing translation of surgical techniques of Le Fort–based facial allotransplantation from swine to humans.

to human cephalometric sellion-nasion–B point) in allotransplants 1 and 2 were −9.7 and −2.8 degrees, respectively. The difference in preoperative and postoperative values for alveolare-pronasale–lower incisor base (analogous to human cephalometric A point–nasion–B point) in allotransplants 1 and 2 were 19.8 and 3.4 degrees, respectively. As in the autotransplant scenario, the parietale-pronasale to occlusal plane angle remained relatively stable postoperatively in the first and second allotransplant scenarios at −2.3 and −2.0 degrees, respectively (Table 3 and Fig. 13, *center*).

DISCUSSION

Face transplantation techniques have evolved from myocutaneous alloflaps to those of osteo-

Fig. 11. Postoperative results, showing translation of surgical techniques of Le Fort–based facial allotransplantation from swine to humans.

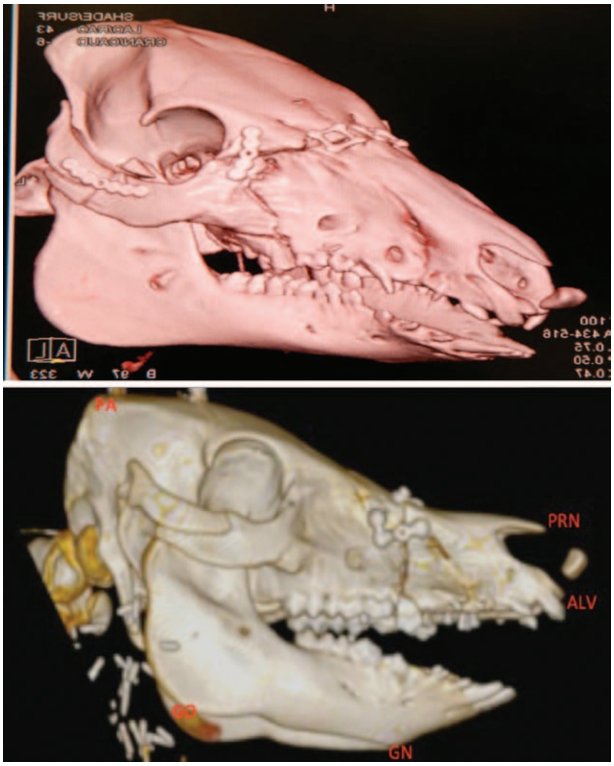

Fig. 12. Postoperative three-dimensional computed tomographic reconstructions. Le Fort III–based facial autoreplantation (*above*) and Le Fort I–based facial allotransplantation in large size-mismatched swine depicting optimal skeletal relation and dental alignment (*below*).

myocutaneous design including the maxilla, nasal bones, zygomas, and mandible.[1] In a properly selected candidate, a maxillofacial transplant can be a viable reconstructive option in the management of complex midfacial defects where autologous reconstructive methods provide suboptimal results. Le Fort–based alloflaps provide not only aesthetic restoration of the facial contour (such as the nose and cheeks) but also restore proper facial dimensions/buttress support, viable teeth, and pertinent functions in the form of facial expression, nasopharyngeal airway patency, restoration of respiratory inflow for olfactory sense, orbital reconstruction, and mastication (Fig. 14).[2]

Donor-recipient matching with regard to facial size, soft-tissue features, skin color, and texture has been shown to be essential for complete facial harmony following transplantation.[14,16] To date, however, all of the reported Le Fort–based, single-jaw transplants have been found to have some degree of dentofacioskeletal discrepancies following transplantation, with some patients requiring orthognathic surgery. This has been manifested as suboptimal donor maxilla-recipient mandibular (e.g., hybrid) occlusion and craniofacial skeletal height deficiencies.[2] Although face transplant surgeons try to match donor-recipient characteristics as closely as possible, rarely can a perfect size match be obtained. This limitation could be addressed partially or fully with computer-aided preoperative planning, allowing for customized surgical techniques and guides, to achieve simultaneous soft- (skin, muscles, and fat) and hard-tissue (skeleton and teeth) aesthetic harmony.[10,14–16] With this in mind, our laboratory began a translational large-animal orthotopic study in July of 2011.[10]

Use of the swine as a large-animal model for orthognathic and other craniofacial surgery is well described in the literature. Anthropometric studies have found the relationship of craniofacial structures such as the pterygoid plates, palatine bones, and maxillary tuberosities to have a similar relationship in the swine as in the human.[6–8] Given these homologous relationships, the swine may be the ideal translational large-animal medium with which to investigate various surgical strategies and improvements, such as preoperative cephalometric planning using three-dimensional computed tomographic reconstruction, live intraoperative image guidance systems, fixation plating strategies, and improved cutting guide design and fabrication (Fig. 15). The goal of developing the aforementioned technologies was to achieve a more ideal posttransplant, donor-recipient craniofacial relationship in swine, which could be successfully translated to the human scenario for various types of complex craniomaxillofacial surgery in both children and adults. (**See Video, Supplemental Digital Content 1**, which demonstrates Le Fort–based, maxillofacial transplantation in size-mismatched swine, and preoperative planning with computer-assisted technology and custom surgical guide fabrication, available in the "Related Videos" section of the full-text article in PRSJournal.com or, for Ovid users, at ***http://links.lww.com/PRS/A972***.)

In designing our study, we first chose to evaluate which craniofacial landmarks would be affected by Le Fort–based facial transplantation. Preoperative and postoperative measurements were taken (Tables 1 through 3). In our study, several landmarks were identified that met the criteria of (1) being readily identifiable preoperatively and intraoperatively with use of computer-aided surgical navigation, (2) conserved postoperatively allowing for accurate cephalometric analysis of postoperative results, and (3) sharing homologous characteristics with the human cranium (Table 1).

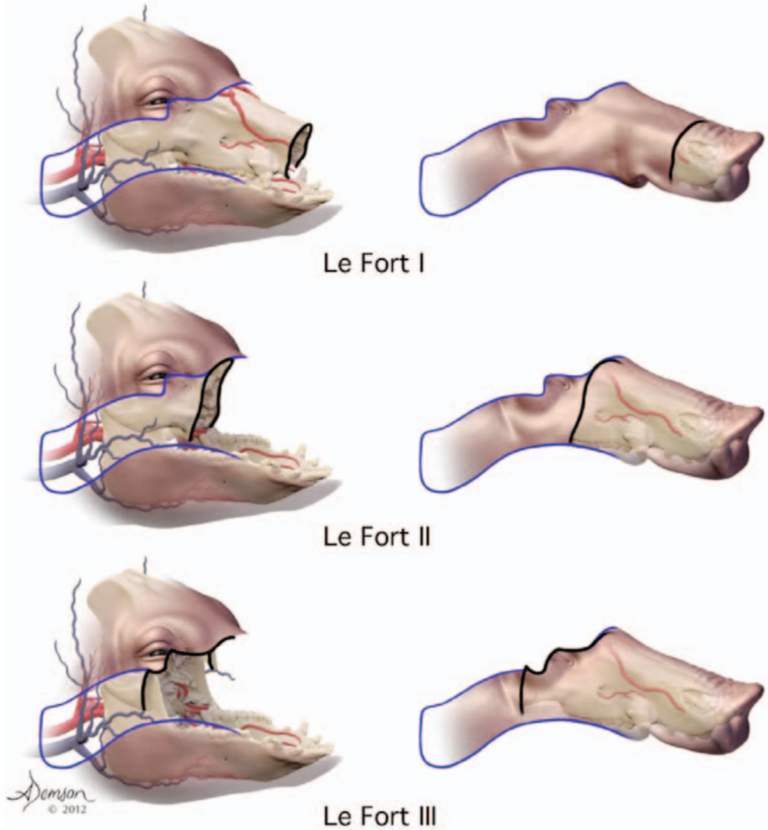

Fig. 13. Schematic diagrams showing various levels of Le Fort–based osteotomies in swine for preclinical investigation. (Printed with permission from Anastasia Demson, M.A.)

A secondary goal of this study was to determine whether we could reestablish the swine's native maxillary-mandibular relationship after performing Le Fort III–based surgery. Our initial autotransplants showed that several useful craniofacial landmarks could be preserved, with relatively close approximation to the native relationship, despite significant craniofacial disruption during transplantation (Fig. 13 and Tables 1 and 2). However, we also found that, even in the autotransplantation scenario, preoperative and postoperative Le Fort–based alloflap placement could be improved by performing computer-assisted surgery and preoperative cephalometric analysis and using prefabricated cutting guides designed specifically with integrated tracking spheres (Fig. 16).

Such improvement can be seen when comparing values of parietale-pronasale-alveolare (sellion-nasion–A point analogue) before and after autotransplantation. Table 3 shows postoperative values of parietale-pronasale-alveolare (sellion-nasion–A point analogue) in the autotransplant scenarios differing by an average of 2.25 degrees. When presurgical cutting guide fabrication and intraoperative live surgical navigation were used in the size-mismatched transplant scenario, recipient and hybrid parietale-pronasale-alveolare

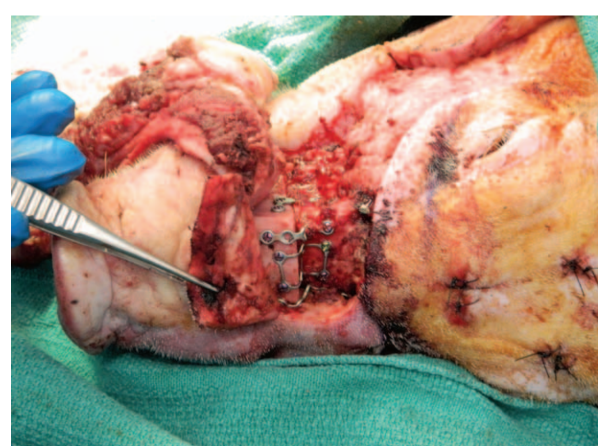

Fig. 14. Bird's-eye view of dorsal maxillary interface between donor alloflap and recipient. The significant dorsal stepoff deformity at the area of osteosynthesis is a consequence of size mismatch, a problem potentially avoided with preoperative assessment with virtual technology.

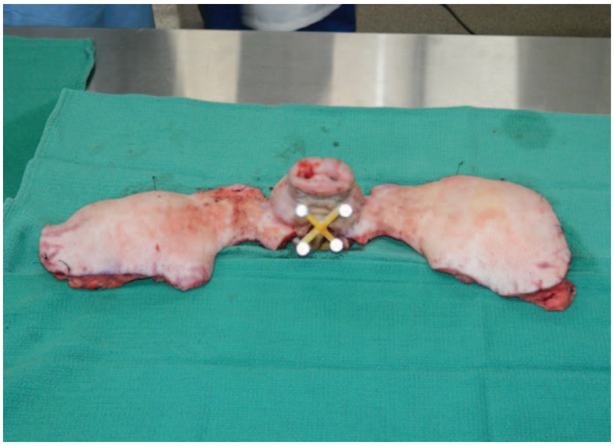

Fig. 15. Facial alloflap, before inset. Real-time surgical navigation hardware is attached to the bony component of the flap.

Fig. 16. Immediate postoperative photograph following successful alloflap inset with adequate perfusion.

Video. Supplemental Digital Content 1, demonstrating Le Fort–based, maxillofacial transplantation in size-mismatched swine, and preoperative planning with computer-assisted technology and custom surgical guide fabrication, is available in the "Related Videos" section of the full-text article in PRSJournal.com or, for Ovid users, at ***http://links.lww.com/PRS/A972***.

discrepancy decreased by 58 percent to only 0.95 degree when compared with the non—computer-assisted, manual reduction. However, this trend in decreased preoperative and postoperative discrepancy did not hold for the other values of parietale-pronasale–lower incisor base (sellion-nasion–B point analogue), alveolare-pronasale–lower incisor base (A point–nasion–B point analogue), or parietale-pronasale to occlusal plane angle when compared with the autotransplant scenarios in Table 3. The increased discrepancies in these values are more attributable to size mismatch than operative technique because the 5-kg swine mismatch had a larger discrepancy in all three of the aforementioned values than the 3.1-kg size-mismatched transplant.

Furthermore, when comparing the postoperative discrepancy between parietale-pronasale to occlusal plane in the autotransplant scenario (where manual reduction of the flap was performed) and the allotransplant scenario (where cutting guides and real-time intraoperative navigation were implemented), the difference was only 0.43 degrees. This illustrates the ability for this technology to maintain some nearly native maxillary-mandibular relationship values (parietale-pronasale-alveolare and parietale-pronasale to occlusal plane), even in the case of significant size discrepancy. Compared with prior swine studies using a single swine model for preclinical craniofacial investigation, we felt that only a transplant scenario between two size-mismatched swine (pairing based on swine leukocyte antigen matching) would be able to provide enough anatomical discrepancies to develop enhanced applications and techniques, and to fully test the technology.[8,18,19] Future studies will compare size-matched and size-mismatched transplants to evaluate the degree of difference this variable contributes to the maxillary-mandibular relationship. We will continue development of computer-aided surgery with implementation of intraoperative real-time cephalometrics to provide on-table prediction of maxillary-mandibular relationships, and prove the superior accuracy that computer-aided planning may offer the craniofacial surgeon.

In defining the relevant cephalometric points, we have established a basis on which these perioperative planning techniques and software technology can be improved, and future results validated. A limitation of the approach described in this article is the reliance on two-dimensional landmarks. Although the surgical planning was completed using three-dimensional imaging techniques, cephalometric analyses were completed using the standard, two-dimensional sagittal view. Our purpose in this regard was to identify reproducible landmarks in the sagittal plane for planning and outcome assessment. Now that we have established that such landmarks are identifiable, our next step will be to identify and validate three-dimensional cephalometric landmarks.

CONCLUSIONS

The numerous morphologic similarities between swine and human skulls allow for the use of swine as an optimal transitional medium to study Le Fort–based maxillofacial allotransplantation. In this study, we identified a new set of reliable cephalometric data points and measurements pertinent for the translational investigation of swine within a preclinical large-animal face transplant model. The use of these craniomaxillofacial landmarks in swine as related to humans, for surgical evaluation and technique development, seems critical for the innovation of computer-enhanced technologies, improved cutting guides, and ability to explore new avenues for investigation and collaboration.

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DISCLAIMER

The views expressed in this article are those of the authors and do not necessarily reflect the official policy, position, or endorsement of the Department of the Navy, Department of the Army, Department of Defense, or the U.S. Government.

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Plastic Surgery Level of Evidence Rating Scale—Prognostic/Risk Studies

Level of Evidence	Qualifying Studies
I	Highest-quality, multicentered or single-centered, prospective cohort or comparative study with adequate power; or a systematic review of these studies
II	High-quality prospective cohort or comparative study; retrospective cohort or comparative study; untreated controls from a randomized controlled trial; or a systematic review of these studies
III	Case-control study; or systematic review of these studies
IV	Case series with pre/post test; or only post test
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Preliminary Development of a Workstation for Craniomaxillofacial Surgical Procedures: Introducing a Computer-Assisted Planning and Execution System

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Introduction: Facial transplantation represents one of the most complicated scenarios in craniofacial surgery because of skeletal, aesthetic, and dental discrepancies between donor and recipient. However, standard off-the-shelf vendor computer-assisted surgery systems may not provide custom features to mitigate the increased complexity of this particular procedure. We propose to develop a computer-assisted surgery solution customized for preoperative planning, intraoperative navigation including cutting guides, and dynamic, instantaneous feedback of cephalometric measurements/angles as needed for facial transplantation and other related craniomaxillofacial procedures.

Methods: We developed the Computer-Assisted Planning and Execution (CAPE) workstation to assist with planning and execution of facial transplantation. Preoperative maxillofacial computed tomography (CT) scans were obtained on 4 size-mismatched miniature swine encompassing 2 live face-jaw-teeth transplants. The system was tested in a laboratory setting using plastic models of mismatched swine, after which the system was used in 2 live swine transplants. Postoperative CT imaging was obtained and compared with the preoperative plan and intraoperative measures from the CAPE workstation for both transplants.

Results: Plastic model tests familiarized the team with the CAPE workstation and identified several defects in the workflow. Live swine surgeries demonstrated utility of the CAPE system in the operating room, showing submillimeter registration error of 0.6 ± 0.24 mm and promising qualitative comparisons between intraoperative data and postoperative CT imaging.

Conclusions: The initial development of the CAPE workstation demonstrated that integration of computer planning and intraoperative navigation for facial transplantation are possible with submillimeter accuracy. This approach can potentially improve preoperative planning, allowing ideal donor-recipient matching despite significant size mismatch, and accurate surgical execution for numerous types of craniofacial and orthognathic surgical procedures.

Key Words: Computer-assisted planning, computer-integrated surgery, cutting guides, maxillofacial transplant, swine facial transplant, craniofacial, craniomaxillofacial surgery, swine study, face transplant

(*J Craniofac Surg* 2014;25: 273–283)

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Facial transplantation is an emerging therapeutic option for patients with complex craniomaxillofacial defects. To date, nearly 25 facial transplants have been reported, with approximately one-third containing underlying facial skeleton and jaw components.[1–3] Operative times for these complex, Le Fort–based facial transplantations can exceed 30 hours.[4–6] However, each previous maxillofacial single-jaw recipient has developed some type of postoperative deformity due to size mismatch and malocclusion between donor and recipient, ultimately requiring revisional surgery.[7] In addition, there are currently no validated methods for optimizing outcomes related to facial (soft tissue), skeletal (hard tissue), and occlusal (dental) inconsistencies in the setting of donor-to-recipient anthropometric mismatch—a major hurdle to achieving this specialty's full potential.[8,9]

Use of computer technology to improve accuracy and precision of craniofacial surgical procedures has been described for nearly 30 years, since the increasing availability of computed tomography (CT) prompted Cutting et al[10] to develop a CT-based surgical simulation plan for osteotomies. Since that time, 2 broad approaches to computer-assisted surgery (CAS) have gained popularity: (1) preoperative surgical planning with the use of three-dimensional printed stereolithography templates (three-dimensional computer-aided design/manufacturing) to guide surgical maneuvers[11–13] and (2) utilizing intraoperative feedback relative to preoperative imaging for the surgeon to provide more objective data on what is happening beyond the "eyeball test."[14,15] Much previous work has described the utility and accuracy of such computer-aided design/manufacturing.[9,11,13,16] However, none are meant for real-time placement feedback in areas where guide placement is more challenging, such as the three-dimensional facial skeleton. To our knowledge, no existing CAS systems are fully satisfactory for the most complicated craniofacial surgeries such as Le Fort–based, face-jaw-teeth transplantation.

Recently, Brown et al[17] described a system including preoperative planning and cutting guides by way of stereolithographic models for human facial transplantation. However, their system (using standard off-the-shelf vendor systems) does not include necessary features to mitigate the increased complexity of this particular procedure. Additional features of interest include (1) intraoperative plan updates based on hard tissue discrepancies between planned and executed procedure, (2) on-table feedback in the form of dynamic, real-time cephalometrics, and (3) trackable cutting guides and predesigned fixation plates matching the virtual plan. Furthermore, in the current CAS paradigms for craniofacial surgery, there is little capacity for intraoperative plan updates. This feature becomes especially important because in some circumstances during the transplantation surgery it may be necessary to revise and update the preoperative plans intraoperatively. The CAS system, therefore, must be robust to deal with situations in which tools and templates designed and fabricated preoperatively may not entirely address intraoperative surgical needs. Robustness of the planning and navigation strategy is especially important in total face transplantation given the long operating times.

Better utilization of advanced surgical technology has potential to improve outcomes and decrease accompanying morbidity via

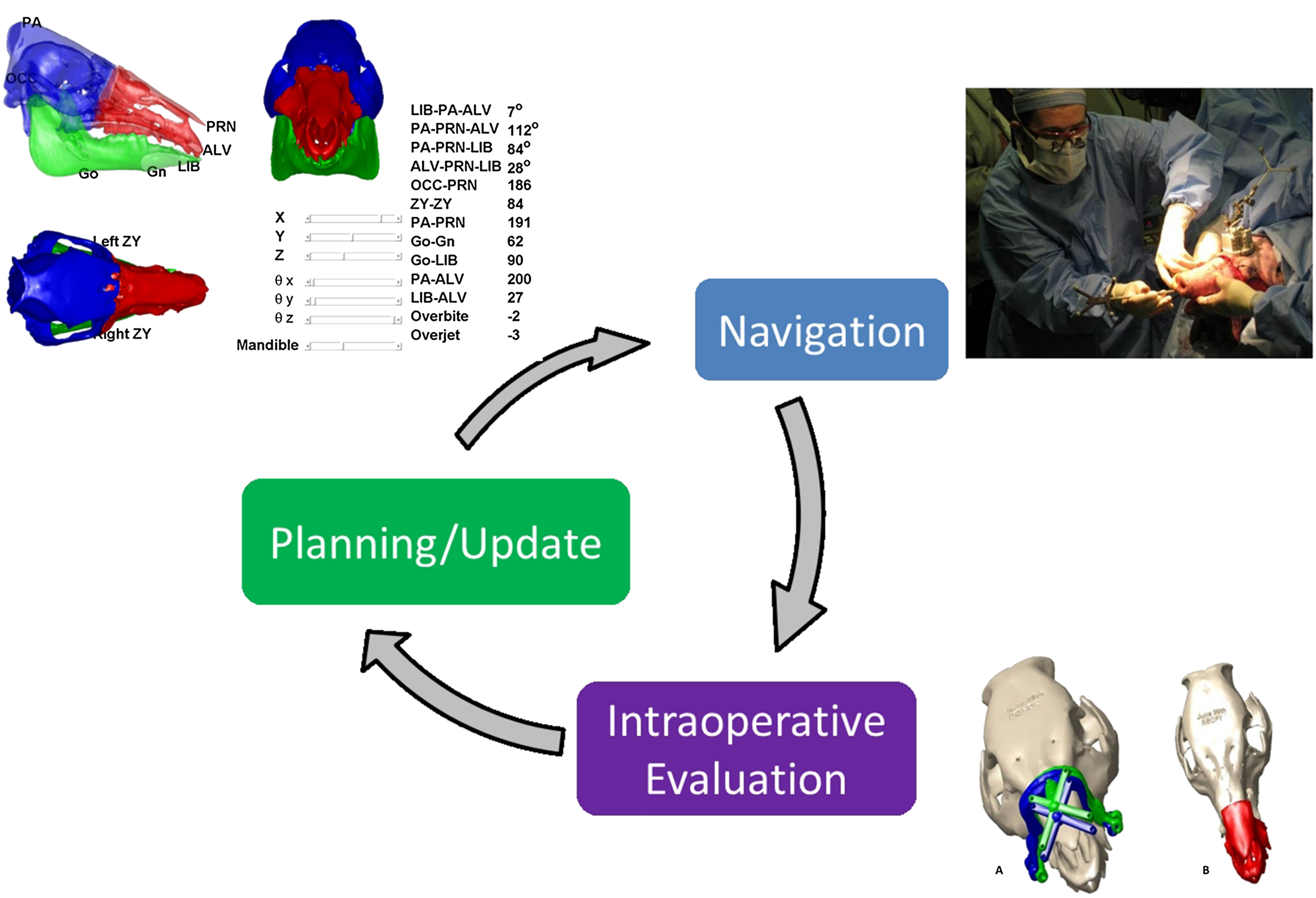

FIGURE 1. Computer-Assisted Planning and Execution improves CAS robustness by closing the loop between planning and navigation and enabling intraoperative updates to the plan with real-time cephalometrics and trackable cutting guides.

shortened operative times, more precise surgical maneuvers, and improved margin of safety. Thus, we developed a CAPE (Computer-Assisted Planning and Execution) system for complex craniofacial surgery such as Le Fort–based, face-jaw-teeth transplantation.[18] This CAPE suite addresses common shortcomings of existing CAS systems as stated in the previous paragraph and has the potential to improve outcomes across both the pediatric and adult-based patient population. The following section describes an overview of the CAPE system and its novel features. The results section reports experiments with the CAPE system on plastic bones and 2 live swine surgeries. It is notable that in a previous study we have performed cadaver studies to evaluate anatomical discrepancies and analogous cephalometric points between swine and human for the purpose of translational investigation.[18]

MATERIALS AND METHODS

The fundamental paradigm for CAS involves developing a surgical plan, registering the plan and instruments with respect to the patient, and carrying out the procedure according to the plan. This paradigm has been reviewed by many for a variety of different surgical procedures.[19–27] In the following, we describe the specific features of the CAPE workstation modules within the CAS paradigm. The CAPE system seeks to increase the robustness of the conventional CAS paradigm by enabling intraoperative evaluation of the surgical plan and providing means for intraoperative plan updates/revisions when needed (Fig. 1).

System Overview

The CAPE system includes integrated planning and navigation modules. The main components of the system are the following: (1) 2 networked workstations concurrently used in planning and navigation of the surgery for both donor and recipient; (2) 2 optical trackers (Polaris, NDI Inc, Waterloo, Canada) tracking bone fragments, tools, and soft tissues (not fully implemented yet) in real-time; (3) novel cutting guides, reference kinematic markers, and so on, as required for navigation (Fig. 2). Preoperative planning involves the following tasks:

- segmentation and volumetric reconstruction of the donor and recipient facial anatomy
- planning for patient-specific cutting guide placement
- cephalometric analysis of the hybrid skeleton
- fabrication of the hybrid cutting guides enabling both geometric (“snap-on” fit) and optical navigation
- mapping the vascular system on both recipient and donor facial anatomy (not completely implemented yet)
- plan updates, if necessary, based on the feedback from the intraoperative module

The intraoperative navigation module changes the conventional procedure as shown in Figure 3. The intraoperative tasks for CAPE include (1) registration of the preoperative model reconstructed from the CT data to donor and recipient anatomy; (2) visualization (using information from the optical tracker) of the instruments and cutting

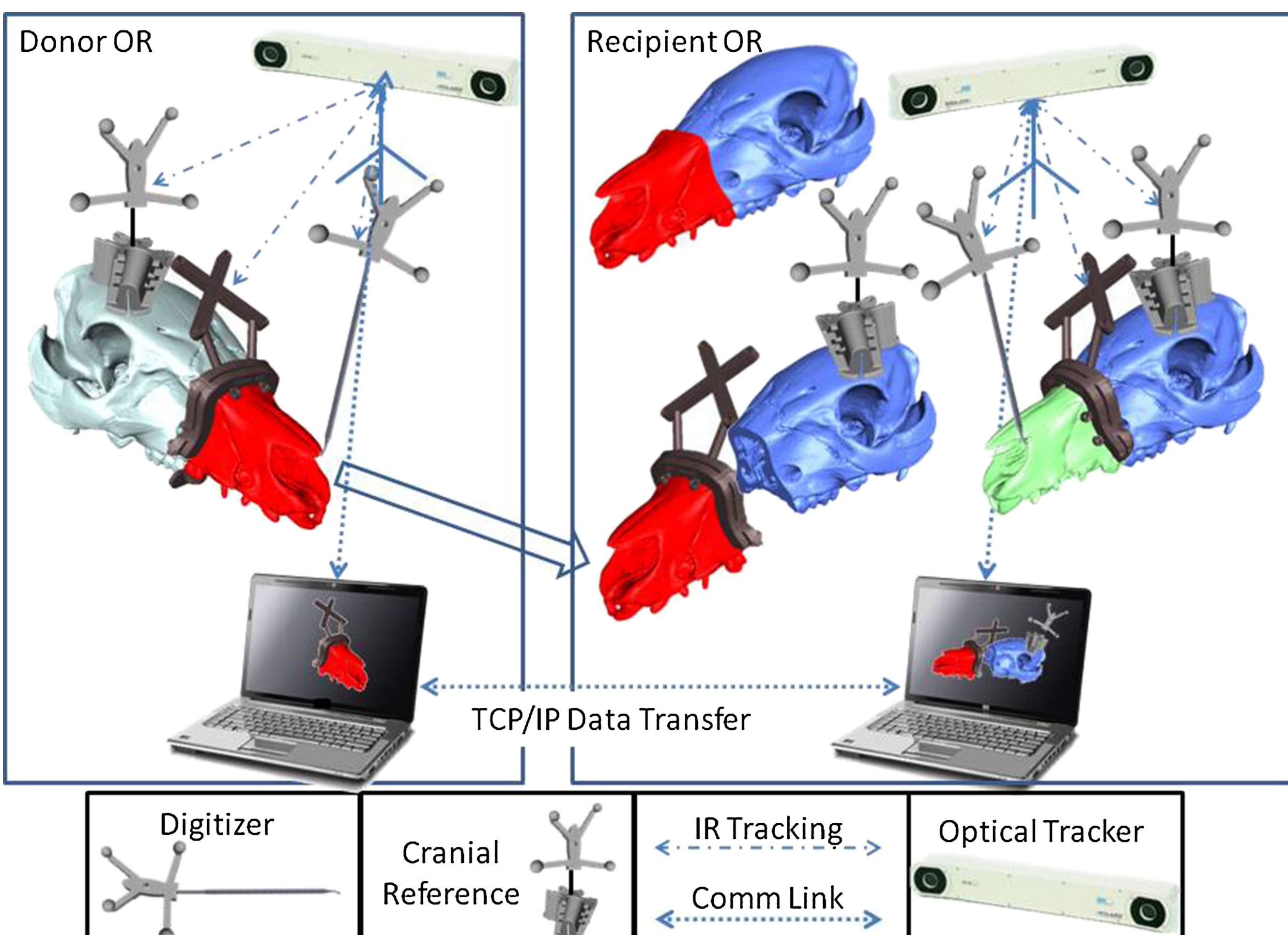

FIGURE 2. The schematic overview of the CAPE and its components.

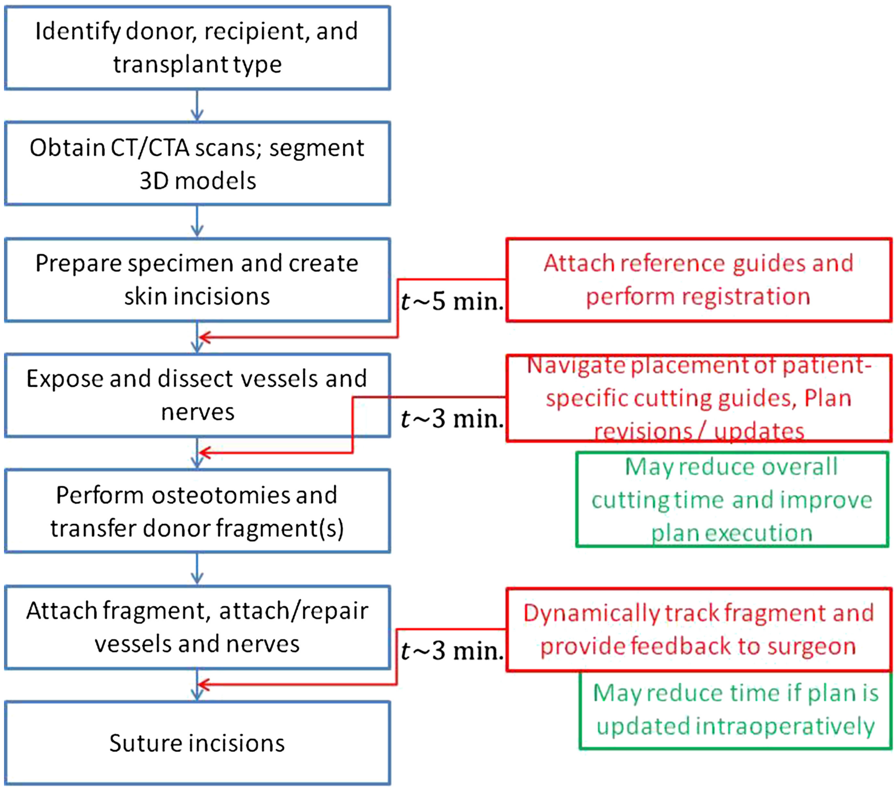

FIGURE 3. The additional procedures associated with the use of the CAPE system (shown in red) and the approximate time taken for each procedure.

guides to help the surgeon navigate; (3) verifying the placement of cutting guides and performing real-time cephalometric and occlusion analysis, if, for any reason, the osteotomy sites need to be revised; (4) dynamically tracking the attachment of the donor fragment to the recipient and providing quantitative and qualitative (visual) feedback to the surgeon.

Preoperative Planning

During the initial planning stage, surgeons determine a virtual plan based on the recipient's craniofacial deformity irrespective of the donor. From registered CT data, segmentation software generates volume data for specific key elements (eg, the mandible, maxilla, and cranium) used for preoperative planning and visualization. The

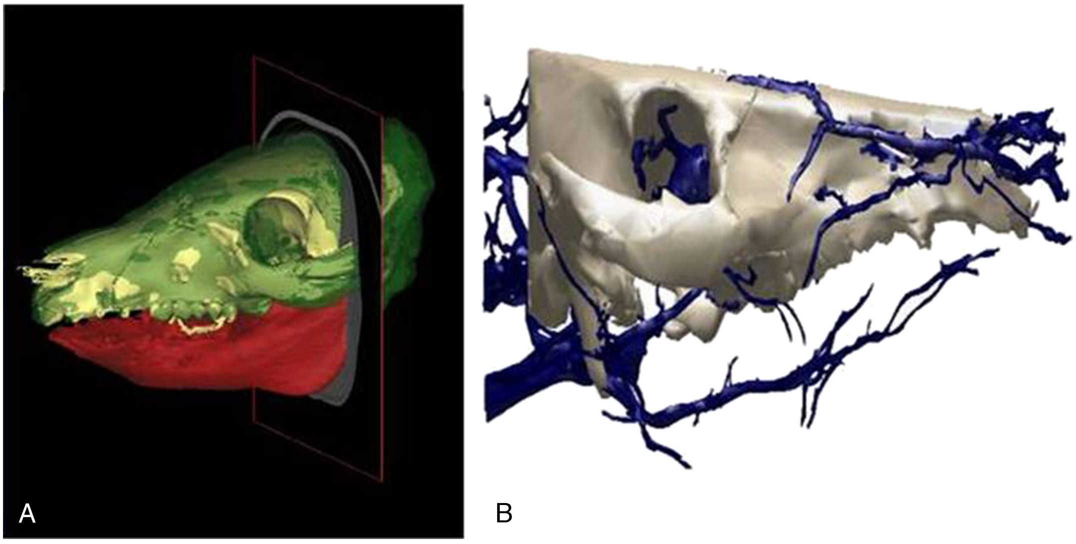

FIGURE 4. A, Computed tomography scan reconstructed images of size-mismatched facial skeleton generated from segmentation software utilized for preoperative planning. B, Segmented arterial system of craniomaxillofacial skeleton generated from CT angiography (CTA) data.

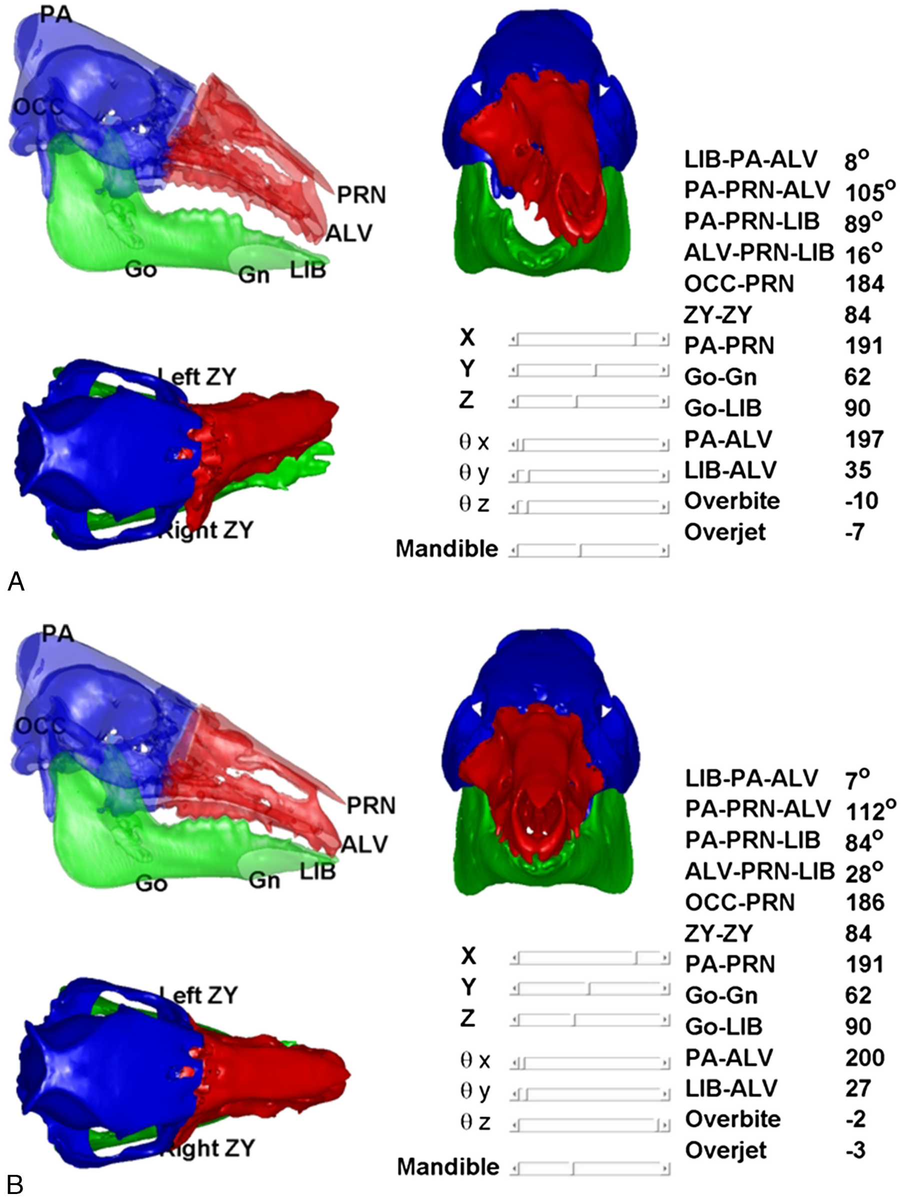

FIGURE 5. On-screen images from CAPE system displaying real-time, dynamic cephalometrics and pertinent measurements applicable to humans for the purpose of translational investigation. Panel A shows donor's face-jaw-teeth alloflap in suboptimal position as compared with recipient's cranium. Panel B shows appropriate face-jaw-teeth positioning with immediate surgeon feedback and updated cephalometric data pertinent to preclinical investigation. The labels and their units of measurements are defined in Table 1.

planning workstation automatically generates the expected cut geometry of the donor fragment together with the recipient, thereby defining the predicted facial skeleton with accompanying hybrid occlusion[2,3,8,18,28] (Fig. 4A). If available, blood vessels are segmented from CT angiography scans (Fig. 4B) to assist surgical dissection.

The planning module also performs static, "best-case scenario," cephalometric analysis and evaluation of face-jaw-teeth harmony on varying constructions of the hybrid donor and recipient jaw (Fig. 5). Using this tool, the surgeon can evaluate different placements for the donor's face-jaw-teeth alloflap on the recipient's face in relation to orbital volumes, airway patency, facial projection, and dental alignment. The automated cephalometric computation for the hybrid face indicates the validity of the planned surgery from both an aesthetic and reconstructive standpoint and may be beneficial for a variety of different orthognathic procedures[8,28] (Table 1). To evaluate and predict cephalometric relationships both during planning and intraoperative environments, the system uses validated, translational landmarks between swine and human.[9,18] The cephalometric parameters defined by these landmarks are automatically recalculated as the surgeon relocates the bone fragments using CAPE's graphical user interface (Fig. 5).

Preoperative planning also involves fabrication of the custom guides and palatal splints. The planned cut planes form the basis for the patient-specific cutting guides, designed with a "snap-on" fit to both donor and recipient. A reference geometry built into the guide structure enables dynamic intraoperative tracking of guides with respect to the patient's skeleton. Palatal splints ensure planned dentoskeletal alignment fixation following Le Fort–type facial transplants. Fixation plates possess eyelets for screw placement to provide rigid immobilization at the irregular skeletal contour areas along

TABLE 1. Pertinent Landmarks for Cephalometric Analysis and Cephalometric Measurements and Related Units

A. Pertinent Landmarks for Cephalometric Analysis

Symbol	Name and Definition
Go	Gonion: a point midway between points defining angles of the mandible
Gn	Gnathion: most convex point located at the symphysis of the mandible
ALV	Alveolare: midline of alveolar process of the upper jaw, at incisor-alveolar junction
LIB	Lower incisor base: midline of anterior border of alveolar process of mandible at the incisor-alveolar junction
PA	Parietale: most superior aspect of skull in the midline, (formed by nuchal crest of occipital bone and parietal bone)
PRN	Pronasale: bony landmark representing anterior limit of nasal bone
ZY	Zygion: most lateral point of malar bone
OCC	Occipital region: midpoint between the occipital condyles

B. Cephalometric Measurements and Related Units

Measure	ZY-ZY	PA-PRN	Go-Gn	Go-LIB	PA-ALV	LIB-ALV	Overbite	Overjet	OCC-PRN	LIB-PA-ALV	PA-PRN-ALV	PA-PRN-LIB	ALV-PRN-LIB
Units	mm	mm	mm	Mm	mm	mm	mm	mm	mm	degrees	degrees	degrees	degrees

various donor-to-recipient interfaces. Having prebent fixation plates decreases total operative times and helps to confirm accurate skeletal alignment (Fig. 6).

Intraoperative Surgical Assistance

Individual navigation for both donor and recipient surgeries tracks the cutting guides with respect to planned positions. Surgeons attach a novel kinematic reference mount to 3 intramedullary fixation (IMF) screws arranged in a triangular pattern on each the donor and recipient craniums (Fig. 7). The mount design permits flexibility in the placement of the IMF screws so that no template is necessary. A spring attaches to each IMF screw via suture threaded through the eyelets. These springs hold the cranial mount in place and allow easy removal and replacement of the cranial mount (eg, during positional changes required for bone cuts and soft tissue dissections). The key design advantages of the reference are detachability and use of IMF screws for stable attachment.

The reference geometry (Brainlab, Westchester, IL) attached to the kinematic mount provides a static coordinate frame attached to the patient. The surgeon digitizes 3 bony landmarks (eg, the inferior aspect of the orbits and anterosuperior maxilla) to define a rough registration between the environment and virtual models. The surgeon collects several point sets from exposed bone using the digitization tool and uses an iterative closest point registration technique to refine the registration.[29] Once registered, the surgeon navigates the placement of the cutting guide using the combination of "snap-on" geometric design and the tracking system coupled to visual feedback (Fig. 8). This allows the team to assess inaccuracies related to soft tissue interference, iatrogenic malpositioning, anatomical changes since acquiring original CT scan data, and/or imperfections in cutting guide design or three-dimensional printing process.

Self-drilling screws affix the cutting guide to the patient's skeleton to ensure osteotomies are performed along predefined planes, maximizing bony congruity. After dissecting the donor's maxillofacial fragment and preparing the recipient's anatomy, the surgical team transfers the facial alloflap. The CAPE workstation tracks the final three-dimensional placement of the Le Fort–based alloflap providing real-time visualization (Fig. 5). This provides real-time visualization of important structures,[7,8] such as new orbital volumes (vertical limit of inset), airway patency (posterior horizontal limit of inset), and facial projection (anterior horizontal limit of inset). Once confirmed, the surgeon fixates the donor alloflap to the recipient following conventional techniques using objective cephalometric guidance.

Development of this technology encompassed 2 separate phases. Phase 1 utilized swine molds and swine cadaver heads for surgical practice. The second phase used 2 live translational surgeries performed on 4 miniature swine (n = 2 transplants) for preclinical experimentation.[9,18]

RESULTS

Overall, several plastic model tests and 2 swine cadaver surgeries helped to familiarize the surgical team in a low-cost and less stressful fashion. Within this phase, team members learned optimal sequences to interact with the intraoperative navigation and repeated various steps for tracking point capture. These iterations resulted in design alterations of the cutting guides to reduce flex and bending for more precise tracking. The novel design (Fig. 8) helped to improve the tracking accuracy from millimeter to submillimeter levels.

Live transplant surgeries (n = 2) between 4 size-mismatched swine (Fig. 9) investigated whether the CAPE suite could actually assist the surgical team in planning and in executing the desired surgical plan. The first live surgery confirmed the proposed utility of

FIGURE 6. Photograph of prebent fixation plates with screw holes and navigational cutting guides provided by the CAPE system for live swine surgery.

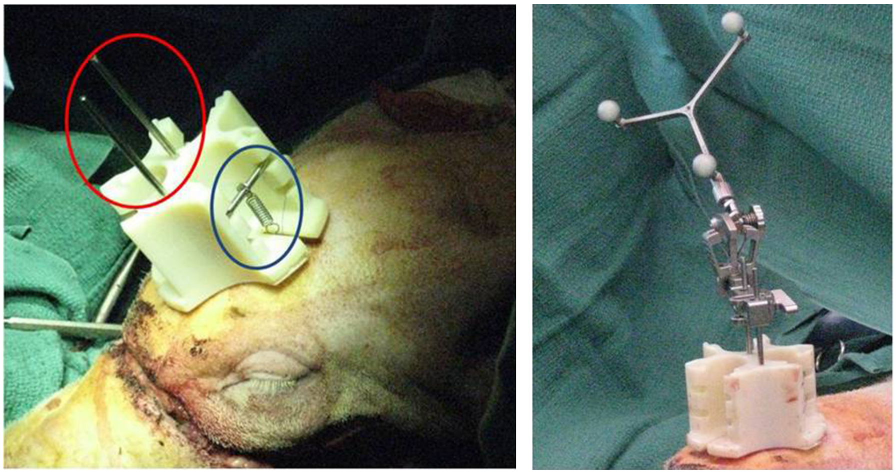

FIGURE 7. A novel kinematic reference mount (red circle) being fixated to donor's cranium with intermaxillary screws. Permanent suture attaches 3 necessary springs and cross bars for stabilization (blue circle) allowing easy removal and replacement during surgery. The photograph on the right shows an ''off-the-shelve'' detachable rigid body (Brainlab) with reflective markers attached to the reference body.

overcoming soft and hard tissue discrepancies related to function and aesthetics[7,8] (Figs. 10A, B). The final occlusal plane within the first recipient was ideal and consistent with the virtual plan as seen on lateral cephalogram (Fig. 10C). Preoperative functional predictions of donor-to-recipient occlusion were realized based on cephalometric analyses performed both before and after surgery. The soft

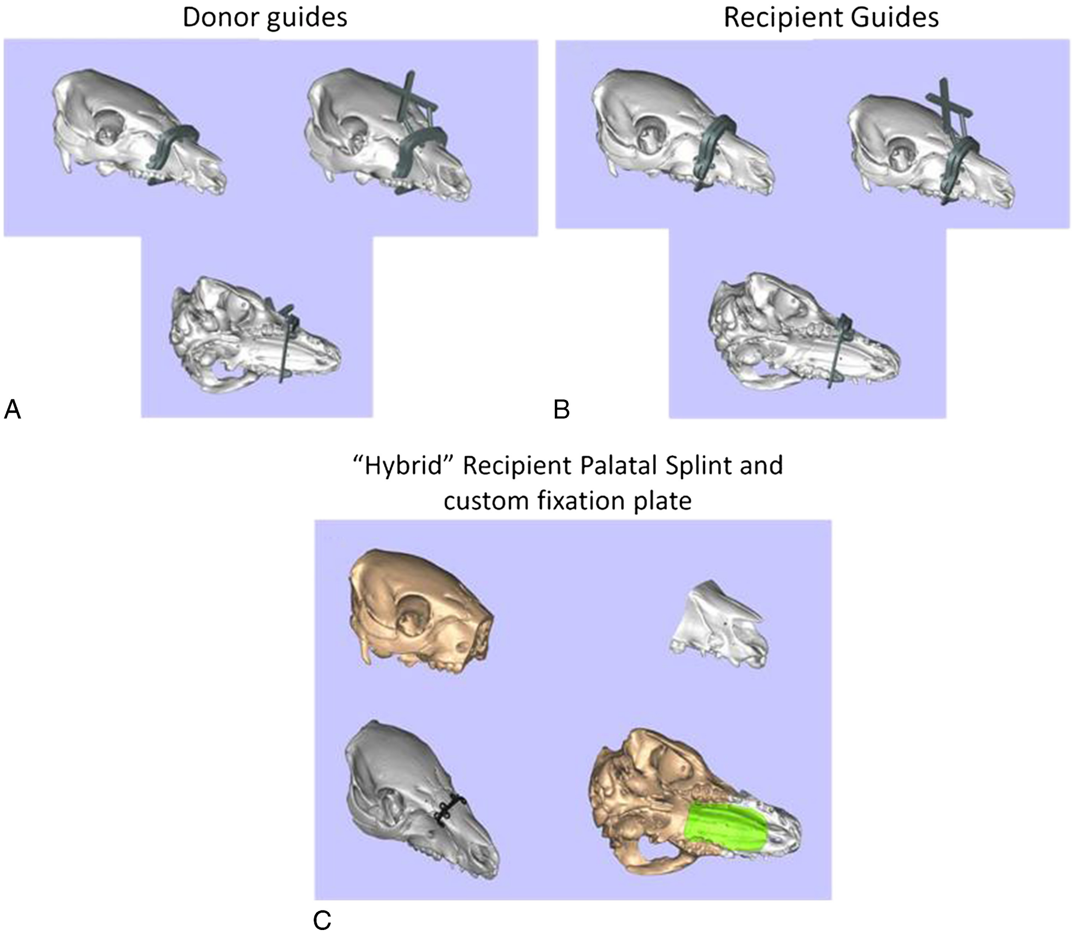

FIGURE 8. Illustrations show novel cutting guide designs with navigational capabilities designed for donor face-jaw-teeth alloflap recovery (A), recipient preparation prior to transplant (B), and custom prebent fixation plate (black) and palatal splint (green) designed to achieve planned face-jaw-teeth alignment and skeletal inset with standard technique (C).

Size-mismatch challenges and discrepancies presented to CAPE system

FIGURE 9. Size-mismatched swine are used for preclinical investigation simulating size discrepancies common to human maxillofacial transplantation. In addition, transplant studies in swine (versus single animal studies) provide our team the most severe challenges related to anatomical discrepancies important for technology development.

tissue inconsistencies of the larger-to-smaller swine scenario were also reduced following the predicted movements of face, jaw, and teeth (Fig. 10D).

The second live surgery showed improved success as compared with its predecessor because of surgeon familiarity and technology modifications. The CAPE system improvements and growing comfort of the surgeons led to reduced operative times for both donor and recipient surgeries. Overall, the surgical time reduced from more than 14 hours to less than 8 hours because of improved surgical workflow (outside CAPE) and increased comfort with CAPE.

Based on the results obtained in the live and plastic bone surgeries (Fig. 2), the functions associated with setting up the CAPE system (attaching references, performing registration, attaching cutting guides) add about 11 minutes to the total length of surgery. However, the overall time can be reduced by minimizing the time required for tracking, locating, and reaching areas of interest during the operation. The overall time for surgery can especially be reduced if information regarding the mapping of vasculature and nerves is presented to the surgeon intraoperatively.

The information recorded from the CAPE suite relating the donor fragment to the recipient qualitatively matched the postoperative

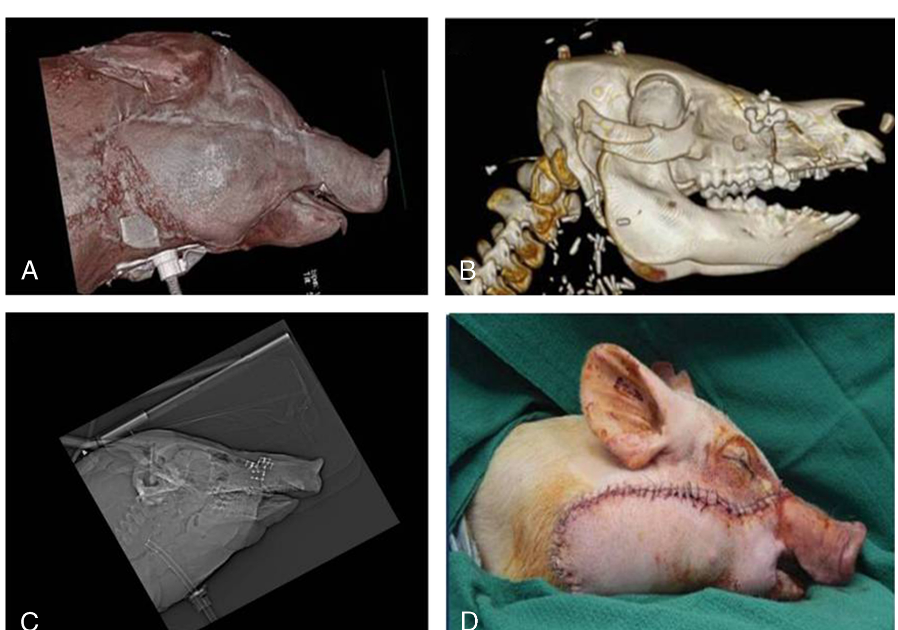

FIGURE 10. Large size-mismatch maxillofacial transplant: (A) profile view of CT scan depicts appropriate soft tissue aesthetic harmony; (B) CT scan depicts skeletal alignment and ''hybrid'' occlusion; (C) lateral cephalogram depicts acceptable cephalometrics; (D) on-table photograph live recipient following face-jaw-teeth transplant inset.

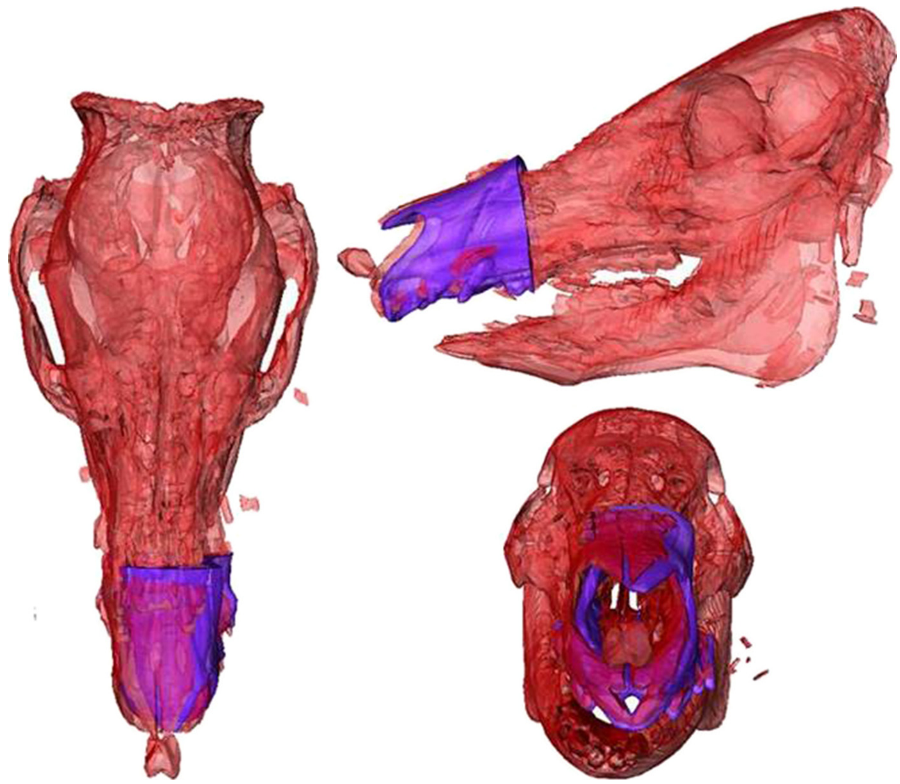

FIGURE 11. Computer-Assisted Planning and Execution system images of transplant recipient skeleton (red) in bird's eye view (left), left-sided profile view (upper right), and frontal view (lower right) depicting real-time assessment of planned (pink) versus actual face-jaw-teeth position (purple).

CT data (Fig. 11). The recipient cutting guide was not placed as planned, however, because of an unexpected collision between cranial reference mount and recipient cutting guide (Fig. 12). In this case, there was anterior translation of the cutting guide (toward the tip of the swine's snout) by approximately 4 cm.

Overall, the donor and recipient craniums (n = 4) were registered successfully to the reference bodies for both live surgeries. The model to patient registration error across the surgeries was 0.6 (SD, 0.24) mm. The novel cutting guide designs proved highly useful in carrying out the planned bone cuts, which compensated for

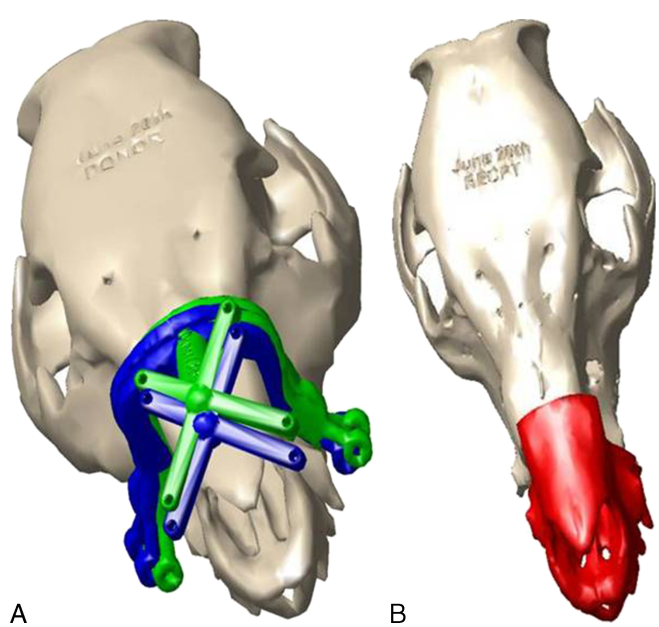

FIGURE 12. ''On-screen'' image from CAPE system depicting ideal location of cutting guide (green) versus actual position (red) (A) and actual inset position of donor alloflap (red) for aesthetic, dental, and skeletal relation in size-mismatched swine because of anterior translation of cutting guide (B).

size-mismatch discrepancies between donor and recipient. Marking spheres fixated to the guides allowed real-time movement tracking and "on-table" alloflap superimposition onto the recipient, thereby allowing visualization of the final transplant result.

DISCUSSION

We developed and demonstrated a single-platform solution, the CAPE workstation, for performing facial transplantation and similar craniomaxillofacial surgical procedures. It provides a preoperative module to define bone cuts on donor and recipient bone models for virtual planning, provides patient-specific three-dimensional designs for cutting guide fabrication/tracking, and tracks the cutting guides and bone fragments during surgery. These benefits provide instantaneous surgeon feedback and the ability to intraoperatively update plans without discarding the CAS system, if surgical plans need modification and/or unexpected obstacles arise.

Compared with previous efforts, this system extends the advantages of CAS beyond that described by Dorafshar et al.[6] This group described using off-the-shelf vendors for navigation and using stereolithographic modeling for osteotomy guidance during double-jaw face transplantation. Although similar, a double-jaw transplant, as reported, is unlike a single-jaw maxillofacial transplant in that it accompanies no concerns for face-jaw-teeth inconsistencies between donor and recipient because the transplanted teeth-bearing jaws are from the same individual. We present here a new platform for preoperative planning and intraoperative predictions related to soft tissue–skeletal–dental alignment with real-time tracking of cutting guides for 2 mismatched jaws of varying width, height, and projection. Additional safeguards, such as collection of confidence points as described below, further enable intraoperative verification of the system accuracy. This, in addition to performing real-time plan verification via cutting guide tracking and real-time dynamic cephalometry, will considerably increase the robustness of the system (Fig. 1). Moreover, the modular nature of the CAPE system allows additional functionality to be continually added.

Plastic bone studies identified areas of improvement and familiarized surgeons with workflow and helped us to identify difficulties. The 2 live swine surgeries tested the system in a true surgical environment and confirmed its efficacy.[18] The outcomes of these surgeries identified the utility of cutting guides coupled with navigation and patient-specific fixation (eg, the palatal splint), and the navigation system is still able to obtain real-time information in the event the guides cannot be placed as planned.

One issue raised from using the navigated cutting guides is the development of an approach for resolving conflicts in case of position discrepancies between the placement of the guide and the guide position prompted by the navigation software. Such discrepancy may be due to either the guide (soft tissue interference, iatrogenic malpositioning, changes since the CT data were obtained or imperfections in cutting guide construction/printing) and/or the navigation system (eg, registration error or unintended movement of the kinematic markers). To resolve these source(s) of discrepancy, we can create 4 indentations on the bone fragment (confidence points) where the reference kinematic marker is attached.[30,31] At any time during the operation, the surgeon can use the digitizer and compare the consistency of the reported coordinates of the indentations via navigation to their coordinates with respect to the virtual computer model.

For development purposes, swine were chosen, given its overwhelming similarities to humans in facial skeletal anatomy and our ability to obtain swine leukocyte antigen–matched animals.[18] An orthotopic, Le Fort–based transplant model was selected to maximally challenge the multidisciplinary team developing the software. This environment provides the most severe cases of aesthetic, skeletal, and dental inconsistencies. In fact, these Le Fort–based challenges are not present in case studies involving just 1 animal, as previously used by other craniofacial laboratories.[32–34] Also, having genetically similar swine (eg, swine leukocyte antigen matched) available for transplantation removes the confounding variables related to immunology and graft rejection, thereby allowing us to concentrate solely of craniomaxillofacial obstacles and technology enhancements.

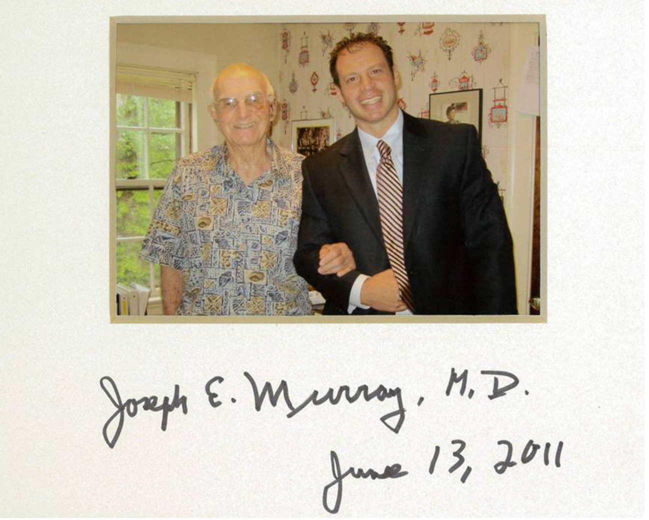

FIGURE 13. A memorable photograph taken within Dr. Murray's office during an inspirational visit to his home in June 2011 (Boston, MA).

Future testing will require rigorous verification and validation studies compared with the preliminary qualitative data presented here. These studies will investigate reliability and repeatability of cutting guide placement comparing navigated and nonnavigated placement. Anecdotal evidence suggests that substantial time reductions for cutting guide placement can be achieved using navigation and that surgeons may be unaware of improper positioning because of soft tissue interference. We plan to develop real-time dynamic cephalometrics and masticatory muscle simulation for both planning and intraoperative guidance as shown in the supplemental video (see Supplemental Digital Content, Video, http://links.lww.com/SCS/A65) in future iterations of the CAPE workstation. Previous work applied to orthopedic surgery could be adapted to assess the hybrid jaw's biomechanical forces and motion resulting from transplant.[30,31,35] Other significant improvements include localizing nerves and vessels to provide the surgeon with a full anatomical "road map" in hopes of decreasing operative times(Fig. 4).

This study demonstrated the potential of the CAPE system for improving safety and long-term outcomes across many areas of complex craniofacial surgery. Development of similar platforms in an open-source research setting will have direct utility for future customization to meet individual applications and surgeon-specific needs.

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C.R.G. would like to dedicate this article in memory of Dr. Joseph Murray, for without his foresight and emphasis on large animal preclinical investigation, together with an intense passion for craniomaxillofacial surgery, none of this would be possible (Fig. 13).

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Restoration of the Donor Face After Facial Allotransplantation

Digital Manufacturing Techniques

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Introduction: Current protocols for facial transplantation include the mandatory fabrication of an alloplastic "mask" to restore the congruency of the donor site in the setting of "open casket" burial. However, there is currently a paucity of literature describing the current state-of-the-art and available options.

Methods: During this study, we identified that most of donor masks are fabricated using conventional methods of impression, molds, silicone, and/or acrylic application by an experienced anaplastologist or maxillofacial prosthetics technician. However, with the recent introduction of several enhanced computer-assisted technologies, our facial transplant team hypothesized that there were areas for improvement with respect to cost and preparation time.

Results: The use of digital imaging for virtual surgical manipulation, computer-assisted planning, and prefabricated surgical cutting guides—in the setting of facial transplantation—provided us a novel opportunity for digital design and fabrication of a donor mask. The results shown here demonstrate an acceptable appearance for "open-casket" burial while maintaining donor identity after facial organ recovery.

Conclusions: Several newer techniques for fabrication of facial transplant donor masks exist currently and are described within the article. These encompass digital impression, digital design, and additive manufacturing technology.

Key Words: 3-dimensional printing, scanning, computer design, AMT, additive manufacturing, craniofacial, binder jetting, materials jetting, mask, donor mask

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Current autologous reconstructive options for devastating midfacial defects, especially those resulting from high-energy trauma, are limited.[1–3] These limitations have led surgeons to adopt alternative methods involving vascularized composite tissue allotransplantation and Le Fort-based, osteocutaneous facial transplantation to achieve better functional and aesthetic outcomes.[4–6] These techniques, although very promising, are still nascent, and considered experimental procedures.

Critical to the advancement of the field, however, is the willingness of potential organ donors, and their families, to agree to donate this complex organ. Facial transplantation, as opposed to internal organ donation, necessarily requires aesthetic destruction of the donor to harvest the facial organ, making an already hard decision increasingly difficult. A recent systematic literature review published by Walker et al found that factors leading families to decide against donation of organs included underlying fears and concerns of violation, desecration, and the donor family member's perceptions of mutilation.[7,8] Additionally, concerns regarding aesthetic destruction and/or disfigurement of the deceased person's body were weighted even more heavily in cases where the potential donor's body seemed unscathed.[9] Given these factors, restoration of the donor's facial appearance after transplantation has become an ethical issue, and in certain countries, a legal requirement, making it an integral component of the facial alloflap harvest procedure.

Various methods of donor facial restoration have been described in the literature; most of which have incorporated various materials and traditional molding techniques to produce donor masks as a means to restore, as closely as possible, the donor's preoperative appearance. Mask materials used in previous facial alloflap donor restorations consisted of acrylic resins and silicone masks.[10,11]

Although detailed descriptions of donor mask production have been mostly absent from the literature discussing donor alloflap harvest, a recent study by Quilichini et al[11] described in detail the process their team used in restoration of the donor's faces after 7 allograft procurements. In their recent paper, they describe the use of alginate to create a mold and impression in negative of the donor's face; a process requiring approximately 30 minutes to complete. This period seems to correlate with what Siemionow and Ozturk[10] and Dorafshar et al[12] have described, and importantly, was not shown to cause any significant delays to the surgical team.

According to Quilichini et al, after the alginate impression is obtained, mask production continues in a separate room, with colored acrylic resins subsequently being poured into the mold. The mask is then refined by makeup application performed by a maxillofacial prosthetics technician or anaplastologist using a photograph of the donor.[11] At the end of the facial alloflap harvest, the mask is positioned on the donor under the surgeon's supervision.[10] Average time of mask production in this series of 7 donor face restoration procedures was approximately 4 hours, and the cost of materials estimated at US $50 per mask.[10] The use of silicone has also been described recently as well for this purpose. Its reported advantages over acrylic resin are lifelike morphologic results and texture; however, this technique will increase the production time[11] (Fig. 1).

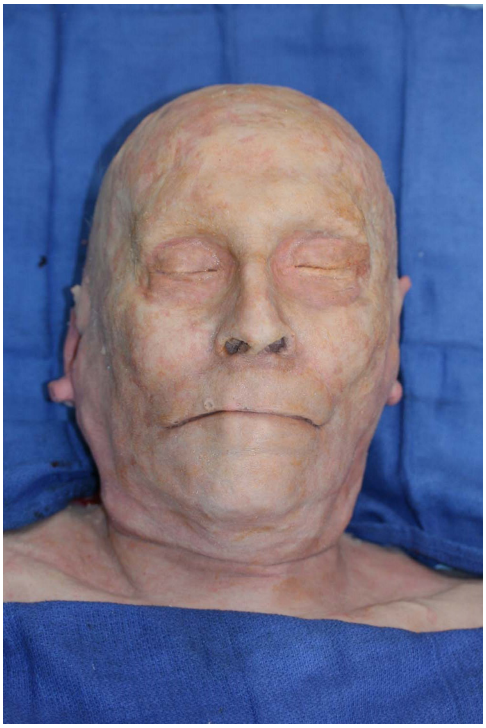

FIGURE 1. Donor mask fabricated from conventional fabrication techniques, note the detail.

Additive Manufacturing Technologies

Although donor mask fabrication by a maxillofacial prosthetic technician or an anaplastologist produces good aesthetic outcomes, some drawbacks do exist with regard to the logistics required to produce the mask, essentially adding a procedure to the surgical day at the donor location before transport. Digital imaging and design software, in conjunction with additive manufacturing (AM) however, provides an avenue to produce a donor mask remote from the site of alloflap harvest. The only prerequisite for this technique is that 3-dimensional surface data must be obtained. These data can be acquired in a multitude of fashions including reconstructions from a medical scan such as computed tomographic (CT) scan, 3-dimensional photography, and/or 3-dimensional scanning.[13–16] The digital representation of the donor's soft tissue can then be modified into a mask and fabricated/manufactured before the graft procedure.

Unlike the conventional impression techniques of using an impression medium such as alginate, plaster, or an elastomeric material, the fabrication of an AM mask is based on imaging of the donor. Digital topography files (.obj, .stl, .vrml) can be obtained from 3-dimensional scanners, 3-dimensional photogrammetry systems, or computational reconstructions from medical imaging system's Digital Imaging and Communications in Medicine files, such as CT or magnetic resonance imaging. These types of files can be digitally modified to develop the final mask/mold file for any AM technology. The detail available in the finished product is related to the resolution of the image and choice of manufacturing process.

The use of medical data to fabricate silicone prosthesis with digital design and AM are already prevalent in the literature for fabricating facial prosthetic devices.[16,17] These same techniques can be applied to donor mask fabrication. To accomplish this, the donor will have medical imaging performed as part of the protocol, so new images may not be necessary for fabrication of a mask. However, a color picture of the patient will be needed to color the mask. The use of a surface scanner is preferred because the quality of the surface texture is independent of slice reconstruction algorithms in medical imaging, and results border on those of a contact impression. Once the digital design of the mask has been established, the next step is to prepare it for the AM device you have selected, based on the application (Figs. 2 and 3).

Direct Binder Jetting

Direct binder jetting is AM technology in which the printer creates the model one layer at a time by spreading a layer of powder (plaster) and printing with a liquid binder in the cross section of the part using an inkjet-like process. Each subsequent layer bonds with the previous and the process is repeated until every layer has been printed, and a full color mask is produced. If this technique is chosen then a color "texture" or mask may need to be added to the digital mask design. Some 3-dimensional scanners and 3-dimensional photogrammetry systems automatically map a picture or multiple picture files to the 3-dimensional surface file if exported as a .vrml or .obj file. If the photograph(s) are not premapped or are not available (ie, CT scan), a digital picture with the face in a similar position can essentially be "wrapped" on the surface of the digital mask (Fig. 4).

The process involves designing, printing, and sealing the mask. This technique requires a minimum amount of "man hours" in that it can be designed and ready for printing in about an hour, the average print time is approximately 4 to 6 hours with approximately 30 minutes of finish time. However, the mask is fabricated from a bound gypsum product that is sealed producing a hard mask that needs to fit directly and securely over the remains of the donor which may be difficult due to skeletal undercuts from the dissected donor area (Fig. 5). In addition, there can be an element of "pixilation" or "stair-stepping" of the surface due to the resolution of the scan, design, or selected printer upon close examination, but color modifications can be made easily with acrylic paints. This method would be appropriate for the fabrication of a full face mask, if the goal of the mask is to preserve the donor's dignity during transportation within the facility, and very limited (distant) viewing is expected.

Indirect Binder Jetting

This is a modification of the previous AM technology; however, instead of printing the mask directly, a mold of the mask is printed, and silicone with custom coloring is "processed" in the mold with a more conventional fabrication method by a qualified maxillofacial prosthetics technician or anaplastologist. This method takes advantage of the digital image to produce a mold, remote from the donor, and before the graft donation. Photographs of the donor are helpful for silicone intrinsic coloring, extrinsic painting, and customizing the mask. Among the advantages of this method are that the mask can be produced in silicone, allowing for control of the thickness. Because silicone is flexible and can be tinted, it is more easily modified for fit and color at the time of application. Also, cosmetic features such as eyelashes and hairs can be added to this type of mask. When properly colorized, such a mask can provide a more "lifelike" appearance; therefore, this technique is more appropriate if there is going to be an open-casket viewing. Production time for this method includes the original 6 to 8 hours to print the mold and another 3 to 4 hours for processing and coloring of the silicone; however, the actual "hands on" fabrication is approximately 4 to 5 hours (Fig. 6). The disadvantages of this method are that much of the detailed surface texture on the mask may need to be recreated due to limited printer resolution. This is done either by overpainting or modifications during the development of the mold, depending upon the resolution of the image capture technique used. However, in the absence of being able to make an onsite impression of the donor, this method represents an alternative method for producing a flexible silicone mask remotely.

Materials Jetting

This is an AM technology similar to binder jetting; however, instead of jetting drops of ink onto a powder; layers of a photopolymer are jetted onto a build tray and cured with UV light. The process continues

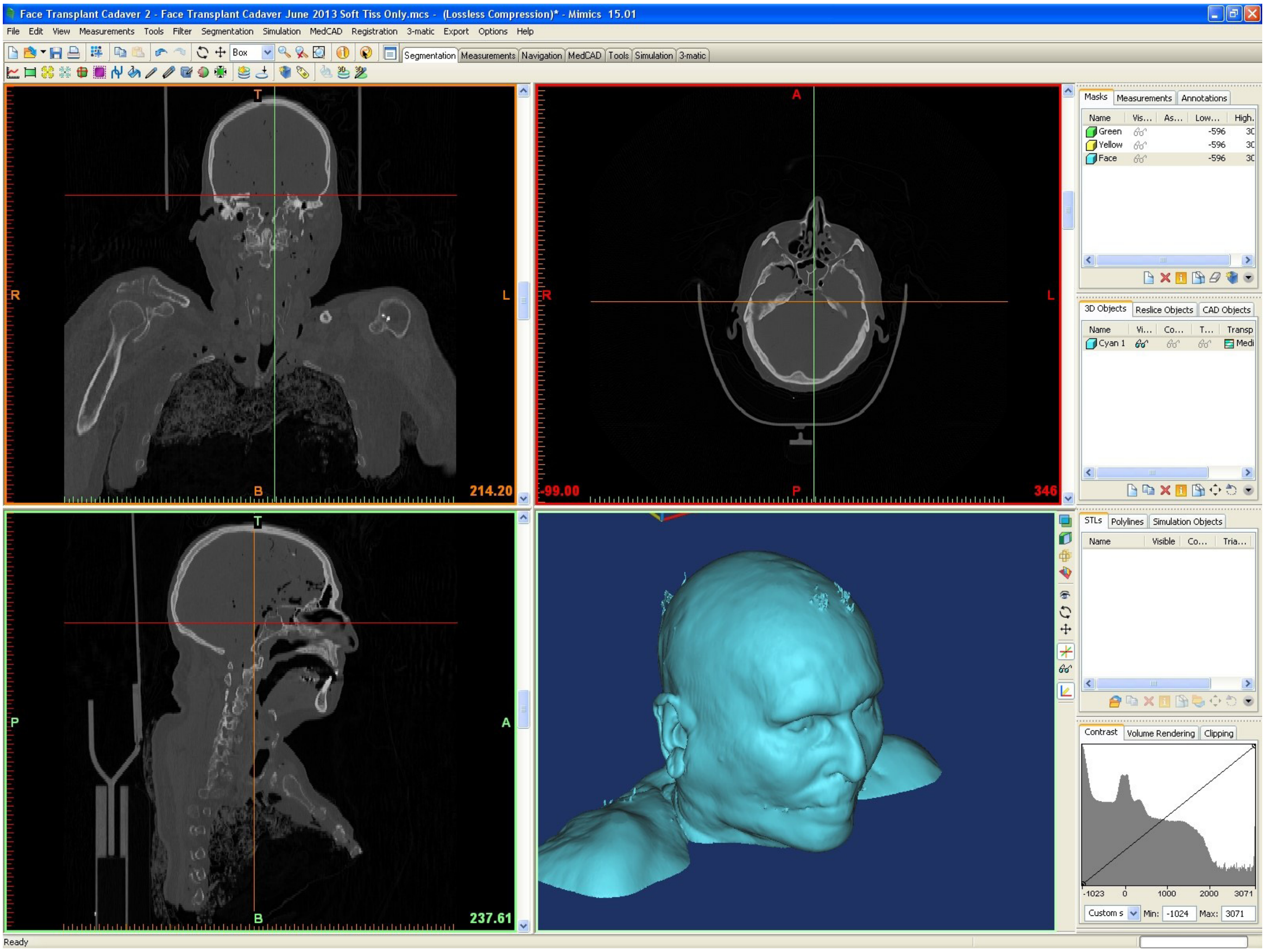

FIGURE 2. Surface geometry is developed from a CT scan.

as the layers are built upon themselves until the mask is complete. The advantage of this system is that you have the availability to produce the mask with multiple materials if desired, both hard and soft which can be manipulated in the build file. This will allow the design of a mask that has the rigidity for support of some structures, but allow for the overall soft "silicone-like" quality. Due to the limited color selections, once the mask has been fabricated, the material is stained to a base shade, and coloring is applied using air brushes and conventional painting methods as needed to highlight features. This can all be performed before any surgical intervention. Design and full production of this polymer mask is approximately 8 to 10 hours and another 1 to 3 hours to colorize the prosthesis. Although some translucency can be maintained by staining the material, the surface texture and translucency of the mask may not match that of the donor due to limited printer resolution and subsequent over painting; therefore, a full mask is recommended.

Sheet Lamination

Sheet lamination is a process in which sheets of a material are bonded to form an object. Recent advances in this technology have resulted in the ability to fabricate a colored object from paper and glue. These printers boast the ability to print in over a million different colors. The product of this technology is similar to that of binder jetting in fabrication time and production of a rigid mask, however, due to the method used to cut the sheets, the surface is generally smooth and does

FIGURE 3. Digital surface impression from CT scan and applied color mask. Note lamination/pixilation lines from a low-resolution CT scan.

FIGURE 4. Direct binder jetted fabricate mask.

FIGURE 6. Indirect silicone masks from printed mold.

not exhibit the "pixilation" or "stair stepping" appearance, unless it is part of the design from a poor resolution scan. In addition, the models colors are easily modified with acrylic paints and can be sealed using cyanoacrylate, resin, or wax. This type of donor mask would have the same issues with skeletal undercuts as other hard material fabrication methods. This is probably one of the most economic methods for fabrication; the raw material is print paper and glue (Fig. 7).

DISCUSSION

Custom fabrication of a donor mask should be a standard procedure detailed within all facial transplant protocols worldwide. Recent advances in virtual surgical planning with digital images have been incorporated in many of these protocols to describe cutting planes and design of surgical cutting guides that are prepared before the procedure. Of note, our team's novel computer-assisted planning and execution system was developed in conjunction with our novel preclinical, swine maxillofacial transplant model.[18–20] The same digital information that is used for these processes can be used to prepare the donor masks as well, streamlining many of the procedures needed on the day of the facial organ recovery. Presently, it seems that the conventional techniques of contact impression, mold fabrication, and direct silicone coloring provide the level of detail required to most closely replicate the donor site and, digital fabrication methods are best indicated for full mask fabrication with limited aesthetics. However, advances in digital capture, digital manufacturing devices, and materials show great promise in that they provides a method to remotely fabricate the mask from captured images and improve print resolutions.

The manner of donor restoration should be based on the wishes of the family, and optimized according to the desired method of posthumous ceremony. As such, the application of digital design and fabrication can be selected to meet that need. For example, if the family would still wish some type of "open-casket" viewing, then custom fabrication in silicone or digital fabrication in silicone would be appropriate. However, if the mask is to preserve the dignity and identification of the donor during transfer within the hospital facility, a printed color mask using direct binder jetting or sheet lamination may be more appropriate and cost effective. Whichever technique is chosen, the technician should ensure that the color, highlights, and details of the mask reflect a more appropriate color palate and opacity more appropriate for a cadaver.

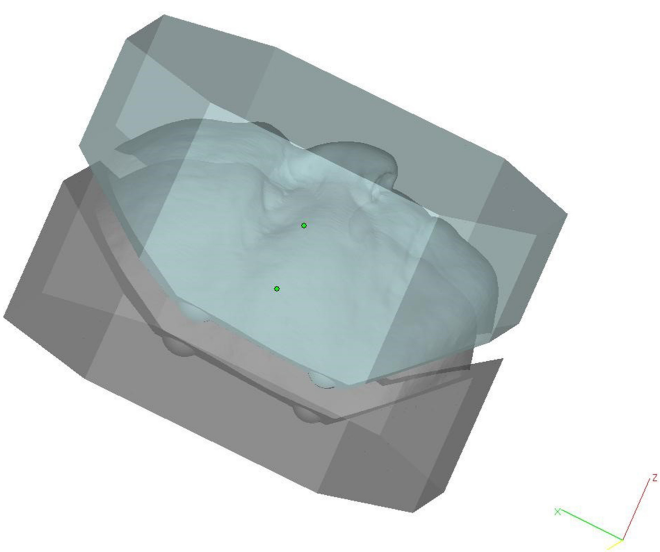

FIGURE 5. Design and printed mold from binder jetting AMT.

FIGURE 7. Sheet lamination fabricated mask. As with the binder jetted mask, note the lamination lines from the low resolution scan.

CONCLUSIONS

By optimizing the technique of donor facial restoration, we hoped to address some of the primary concerns families encounter when having to make a decision to offer their loved-one's face as a donation. Presently, custom conventional fabrication of donor masks by an experienced maxillofacial laboratory technician or anaplastologist has some advantages over AM techniques. However, it is important to know that AM technology has been shown to produce an aesthetically acceptable prosthetic result, as presented here. Digital capture of the donor and design of the masks should account for many of the more detailed features and provide for secure application of the mask, as well as restore the congruency of the donor site. The present state of technology, to develop the impression and manufacture a mask using digital tools, is still in its developing stages and offers variety in the approach to be used. As AM technologies improve in their ability to model better resolutions, improve the ability to add color directly to the materials, and obtain 3-dimensional capture capabilities, the present gap between custom and digital fabrication techniques may be indistinguishable. Irrespective of the fabrication technique chosen, the prosthetic restoration of a donor's face is integral to the facial transplantation procedure to ensure that greatest respect is paid to the deceased.

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ORIGINAL ARTICLE

Computer-assisted, Le Fort-based, face–jaw–teeth transplantation: a pilot study on system feasiblity and translational assessment

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Abstract
Purpose Le Fort-based face–jaw–teeth transplantation (FJTT) attempts to marry bone and teeth geometry of size-mismatched face–jaw–teeth segments to restore function and form due to severe mid-facial trauma. Recent development of a computer-assisted planning and execution (CAPE) system for Le Fort-based FJTT in a pre-clinical swine model offers preoperative planning, and intraoperative navigation. This paper addresses the translation of the CAPE system to human anatomy and presents accuracy results.
Methods Single-jaw, Le Fort-based FJTTs were performed on plastic models, one swine and one human, and on a human cadaver. Preoperative planning defined the goal placement of the donor's Le Fort-based FJTT segment on the recipient. Patient-specific navigated cutting guides helped achieve planned osteotomies. Intraoperative cutting guide and donor fragment placement were compared with postoperative computed tomography (CT) data and the preoperative plan.
Results Intraoperative measurement error with respect to postoperative CT was less than 1.25 mm for both mock transplants and 3.59 mm for the human cadaver scenario. Donor fragment placement (as compared to the planned position) was less accurate for the human model test case (2.91 mm) compared with the swine test (2.25 mm) and human cadaver (2.26 mm).
Conclusion The results indicate the viability of the CAPE system for assisting with Le Fort-based FJTT and demonstrate the potential in human surgery. This system offers a new path forward to achieving improved outcomes in Le Fort-based FJTT and can be modified to assist with a variety of other surgeries involving the head, neck, face, jaws and teeth.

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Keywords Face–jaw–teeth transplantation · Face transplant · Le Fort-based transplant · Surgical cutting guide · Navigation · Preoperative planning

Introduction

Le Fort-based face–jaw–teeth transplantation (FJTT) is an emerging alternative for reconstructing patients with severe craniomaxillofacial (CMF) disfigurements non-amenable to conventional methods of reconstruction [1–4]. The experimental procedure utilizes both hard and soft tissue from a brain-dead cadaveric donor to replace damaged portions of a recipient's face, analogous to solid organ transplant. Recipient trauma sources have included ballistic wounds, blunt trauma, cancer, and animal attack [3–7]. Each combination

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of size-mismatched, donor and recipient anatomy presents unique challenges for both optimal function and appearance. To date, only ten Le Fort-based FJTTs (those face–jaw–teeth transplants which include the underlying facial skeletal structures such as zygomas, maxillae, orbital floors, palate, and teeth) have been performed worldwide [4]. While deemed successful, all single-jaw transplant patients have required some form of revision surgery after undergoing FJTT due to suboptimal donor-to-recipient dental alignment. Preliminary evidence suggests accurate dento-skeletal alignment in FJTT, including hybrid occlusion for opposing dental arches, is a very difficult part of this surgery [1,3,4,6,8]. As such, Le Fort-based FJTT will remain limited until this particular obstacle can be overcome.

Computer-assisted surgery (CAS) leverages patient models for preoperative planning and intraoperative navigation, guidance, and (possibly) real-time plan updates [9,10]. Many surgical procedures within similar fields like CMF surgery, head and neck surgery, ear/nose/throat (ENT) surgery, and neurosurgery have seen advances through CAS [11–15]. Recent developments in additive manufacturing technology (AMT), more commonly known as 3D printing, have enabled the use of patient-specific guides in a variety of dental and craniofacial procedures [11,14,16–18]. Accordingly, the combination of these paradigms may have extensive use in Le Fort-based FJTT and other orthognathic procedures, through more appropriate dento-facial-skeletal alignment and surgical accuracy resulting in improved outcomes.

Recent research describes a computer-assisted planning and execution (CAPE) workstation for assisting surgeons during Le Fort-based FJTT [19,20]. The goal was to develop a system that combines preoperative planning with intraoperative navigation and biomechanical guidance using patient-specific surgical cutting guides and optical navigation. This system should include unique features including real-time, intraoperative cephalometric analysis and preoperative biomechanical simulation for predicting donor-to-recipient jaw relation/motion post-transplant [21]. It is notable that the current state of the art commercial systems (e.g., Stryker Craniomaxillofacial, Stryker, Kalamazoo, MI, USA; Synthes Craniomaxillofacial, Synthes, West Chester, PA, USA) and reported (noncommercialized) systems in literature [8,11,22] do *not* have the full suite of features developed for the CAPE system. The synthesis of these diverse features within the CAPE system may offer potential to improve accuracy and reduce operating times (reported FJTT transplant times exceed 14–30 h) over existing systems, which may lead to better patient outcomes and potentially prevent the need for revision surgery.

The pre-clinical CAPE system was initially developed and tested on swine (both cadaveric and live), without incorporating human anatomy from 3D plastic models or cadavers [19,20,23]. As such, this paper addresses the translational capabilities of the CAPE system as applied to human anatomy through mock transplants performed on human plastic models and a single-human cadaver transplant. Moreover, comparison of planned osteotomies and placement of the donor fragment identified the intraoperative accuracy of the CAPE system with respect to postoperative imaging data. A discussion on the results concludes the paper, remarking on the potential for the CAPE system to be used for Le Fort-based FJTT.

Materials and methods

System overview

The CAPE system, fully described by Gordon et al., provides planning and navigation for Le Fort-based FJTT [20]. This overview focuses on a single-jaw–teeth transplant to also address the more challenging problem of hybrid occlusion (i.e., improper teeth alignment and contact). Hybrid occlusion does *not* exist for those facial transplants (1) containing only soft tissue components and (2) containing both upper and lower jaw/teeth segments from the donor. The procedure varies slightly for different transplant routines depending on the extent of the recipient's disfigurement, but the majority of steps are consistent between surgeries for all single-jaw, Le Fort-based maxillofacial transplants.

Prior to surgery, a cadaveric donor is identified for a specific recipient in need of maxillofacial restoration. Once identified, the donor face should be harvested and transplanted within 48–72 h. Standard computed tomography (CT) scans of the donor and recipient are acquired. Segmentation of the CT data defines a set of three-dimensional volumes and surface models of relevant skeletal anatomy, which includes the cranium, upper jaw (maxilla), lower jaw (mandible), and teeth. The surface models provide visualization throughout the surgery and are the main components in the planning stage.

The donor and recipient models and CT data are manually aligned based on the type and extent of surgery, and expected osteotomy pattern (Fig. 1). For patients requiring single-jaw restoration, the surgeon's main focus is on achieving rigid, stable alignment of the cranium, jaw, and teeth; this includes analysis of the hybrid occlusion to ensure appropriate alignment. (The skeletal alignment dictates the final position of the overlying facial soft tissues—skin, muscle, and fat—and ultimate appearance.) The bony alignment of the models provides a common coordinate frame between the donor and recipient. Once aligned, the surgical team plans the surgery by identifying appropriate cutting planes on the recipient based on anthropometric differences [19]. These cutting planes are based on the type of surgery necessary (i.e., Le Fort I, II, or III) and generally follow predictable

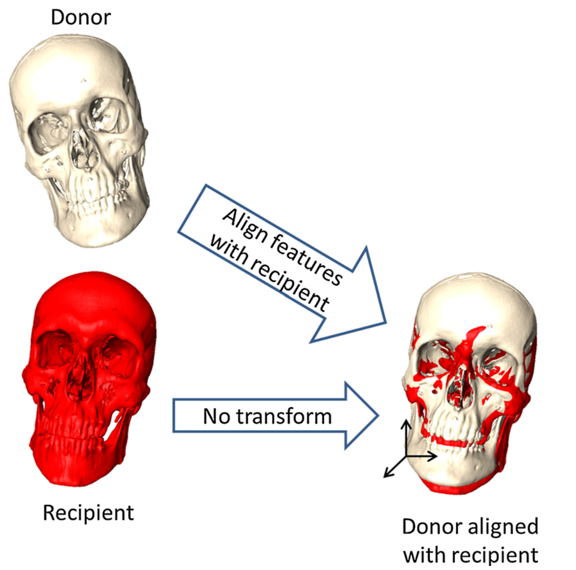

Fig. 1 Alignment of the donor and recipient surface models. The combined surface model has a common coordinate frame between the donor and recipient

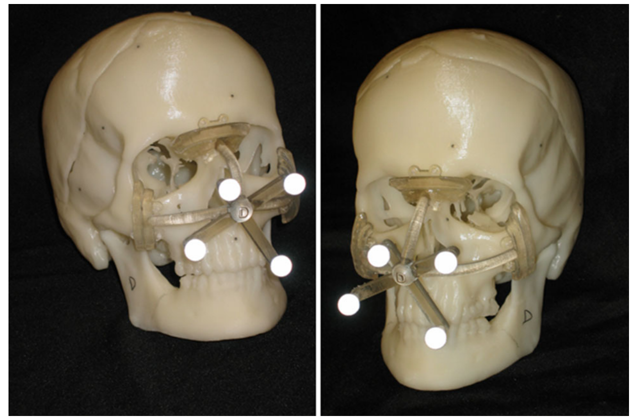

Fig. 2 Patient-specific cutting guides on donor specimen with an attached reference geometry. The reference geometry is tracked through the environment by the four spheres, which reflect infrared light

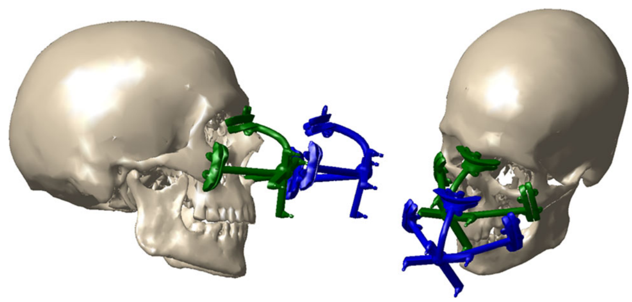

Fig. 3 The patient model display of the CAPE system with the planned position of the guide (*green*) and the actual position of the guide (*blue*) during guide placement

fracture patterns of the face. Curved cuts, while possible, will not follow these natural fracture patterns exhibited in the face and are more difficult to perform. The alignment of the donor and recipient models facilitates the transfer of the cutting planes identified on the recipient to analogous positions on the donor.

After identifying the goal cutting planes preoperatively, patient-specific cutting guides are designed and fabricated. The form-fitting cutting guides offer a precise fit to the bone and ensure the surgical cuts are performed at the appropriate location and angle. Integrated in the design of the geometry of the cutting guide is a rigid structure for optical tracking that does not interfere with the surgeon's cutting routine. Patient-specific guides are fabricated with the appropriate AMT processes for surgery (Fig. 2).

The initial surgical routine is identical for both the donor and recipient. First, a reference geometry is attached to the cranium. The reference geometry is visible to the optical tracker (Polaris, NDI Inc., Waterloo, Canada) and provides a static frame on the patient. A pointing tool digitizes a set of anatomical landmarks on the patient that were previously selected on CT scans (e.g., the most inferior/anterior point on the infraorbital rim and bridge of the nose for humans) to define a gross registration between the patient and the segmented surface model. Tracing the pointing tool along the exposed bone provides input to an iterative closest point [24] algorithm to obtain a more precise registration between the patient and the model. The cutting guides are attached to the patient and the navigation system reports on the alignment accuracy (Fig. 3). The surgeon uses the cutting guides to easily achieve the preoperative plan, extracting the planned donor fragment and removing the recipient's defect to assure congruency.

In the single-jaw FJTT, the donor fragment is mainly the maxilla, while the recipient retains the cranium and mandible with teeth. The donor fragment is moved to the recipient operating table following neurovascular dissection. The cutting guides are designed such that after cutting, the donor fragment is still rigidly fixed to the attached reference. This allows the surgeon to track the movement of the donor fragment with respect to the recipient with visual feedback during placement. As the surgeon places the donor fragment, the CAPE system informs the surgeon of the placement accuracy (Fig. 4) and computes real-time, hybrid cephalometrics and occlusion [20,25] (Fig. 5). Cephalometric analysis computes angles and distances between well-established human dento-skeletal landmarks, or their swine analogs [25] (Tables 1, 2; Fig. 5), to quantify facial harmony, esthetics, and occlusion [26]. The landmarks are identified preoperatively on both the donor and recipient jaw–teeth fragments and distance/angle measurements are computed automatically. Following visual confirmation, the surgeon ensures the fragment placement is appropriate and rigidly fixates the donor jaw–teeth to the recipient cranium using a standard set of titanium plates and screws.

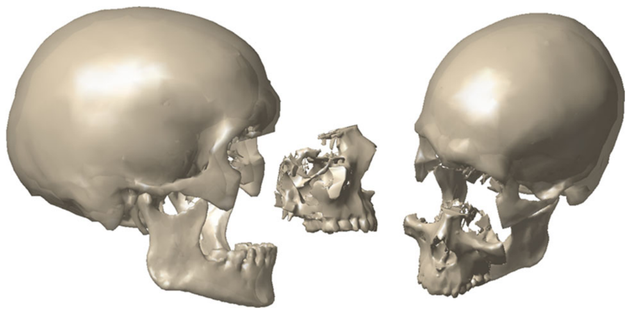

Fig. 4 The CAPE system visualizes the donor fragment as it is placed onto the recipient

Table 1 Human and swine cephalometric landmarks [25]

Human landmark	Swine landmark
Gonion (Go)	Gonion (Go)
Nasion (N)	Pronasale (PRN)
A point (A)	Alveolare (ALV)
B point (B)	Lower Incisor Base (LIB)
Sella (S)	Parietale (Pa)
Menton (M)	Gnathion (Gn)
Left/right Zygoma (ZY)	Zygion (Zy)
Os occipitale (OCC)	Os occipitale (OCC)

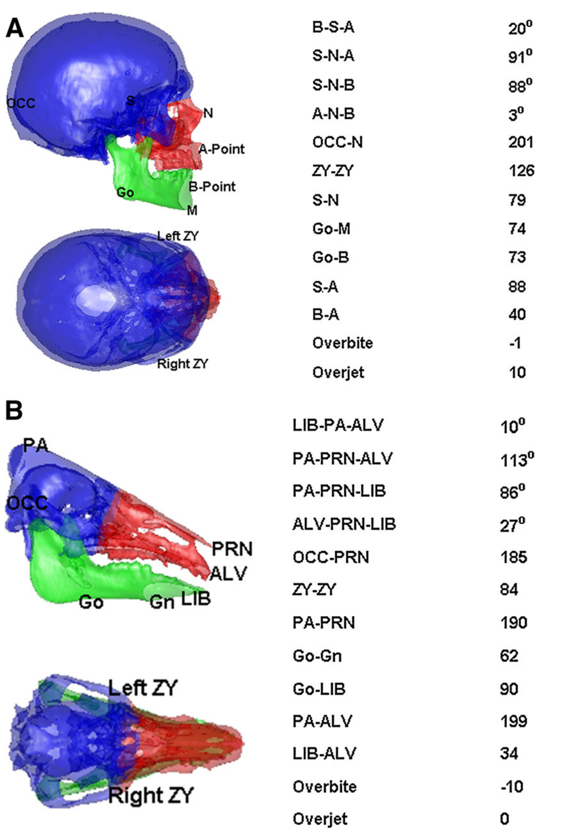

Fig. 5 Example real-time cephalometric display provided by the CAPE system to the surgeon for both human (**a**) and swine (**b**). This display is updated as the donor jaw fragment is moved with respect to the recipient cranium, and the cephalometric parameters are reported to the surgeon. Distances between points are measured in mm and angles are measured in degrees

Table 2 Definition of the cephalometric measurements

Measurement	Definition
B–S–A	Angle between the B point, sella, and A point
S–N–A	Angle between the sella, nasion, and A point
S–N–B	Angle between the sell, nasion, and B point
A–N–B	Angle between the A point, nasion, and B point
Occ–N	Distance between the os occipitale and the nasion
Zy–Zy	Distance between the left and right zygomas
S–N	Distance between the sella and the nasion
Go–M	Distance between the gonion and the menton
Go–B	Distance between the gonion and the B point
S–A	Distance between the A point and the sella
B–A	Distance between the A point and the B point
Overbite	Vertical overlap between upper and lower teeth
Overjet	Horizontal overlap between upper and lower teeth

Experiment overview

Two mock FJTT surgeries (one using swine anatomy, one using human anatomy) performed on plastic models tested the CAPE system. Each mock surgery used existing CT data (live-animal or cadaveric) as the basis for constructing the plastic models. An additional surgery was performed on a human cadaver using donor and recipient specimens obtained from the Maryland State Anatomy Board. For the swine surgery, the recipient was chosen as the smaller of the two in the setting of a large size mismatch. The donor and recipient for the human studies were arbitrarily chosen from the specimens obtained through the Maryland State Anatomy Board.

Commercial software (Mimics, Materialise, Leuven, Belgium) aided in the semi-automated segmentation and labeling of various hard tissue structures on preoperative CT data. An automatic threshold segmentation identified the bony anatomy. Manual adjustments refined the segmentation and separated the cranium and maxilla from the mandible, generating distinct surface models. Stereolithographic models made of resin (Acura ABS White, SLA 7810, 3d Systems, Rock Hill, SC, USA) were fabricated for the surgeries with high accuracy [27]. After printing, radiopaque fiducials (stainless steel beads) were implanted on the specimen in sets of (at least) four to serve as the ground truth for fragment movement. Each set of beads was placed on bony anatomy of interest (i.e., the maxilla or cranium) to facilitate post-operative registration (Fig. 6). Using small spherical beads (1.5–2.2 mm diameter) reduced metallic artifact in the sub-

Fig. 6 Printed plastic human skull (recipient) with fiducials attached and simulated trauma

sequent CT scans and did not interfere with model segmentation or reconstruction.

Prior to each FJTT surgery, virtual planning was performed according to the CAPE protocol. The models were CT scanned at $0.45 \times 0.45 \times 0.6$ mm resolution on a SOMATOM Definition Flash scanner (Siemens Healthcare, Germany). The scans were performed at 100 kVp, with a tube current of 421 mAs (human cadaver) or 566 mAs (plastic model). A soft tissue reconstruction kernel was used. These imaging protocols are appropriate for real patients and were shown to be effective in the human cadaver surgery. Clinically, ideal slice thickness is 1.25 mm or less. Both the anatomical structures (i.e., cranium and mandible) and the fiducials were segmented from the preoperative model, which had been created using CT data. After defining the cutting planes based on donor-to-recipient hybrid relation, patient-specific guides were designed using commercial software (FreeForm Plus, 3d Systems, Rock Hill, SC, USA; Magics, Materialise, Leuven, Belgium). The guides were printed on a Connex 500 printer (Stratasys Ltd., Eden Prairie, MN, USA) using biocompatible material (Objet Med610, Stratasys Ltd., Eden Prairie, MN, USA) (Fig. 2). The material chosen for this study allowed some structural flexibility in the guides during the swine scenario to improve positioning prior to final placement with screw fixation. Of note, this flexibility is not considered necessary in human operations but was found useful in the swine.

The surgeries followed the CAPE routine with the additional steps to analyze the donor fragment placement. Using the optical tracker, the CAPE system recorded the fixed position of the donor guide relative to the donor maxilla and the recipient guide relative to the recipient cranium. As the surgeon placed the donor fragment onto the recipient, the optical tracker acquired a "snapshot" of the unfixed relative position of the donor guide (and, by association, the donor fragment) on the recipient's cranium. The surgeon then fixated the donor fragment in place using plating fixtures (Stryker Universal Fixation System). Hot glue also helped to reinforce the final maxilla fragment position within the human mock scenario in addition to the rigid titanium plate fixation (Fig. 7).

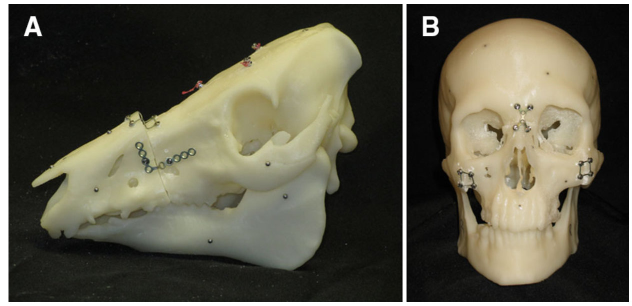

Fig. 7 Final placement of donor jaw–teeth segment onto the recipient's cranium/mandible for (**a**) swine and (**b**) human

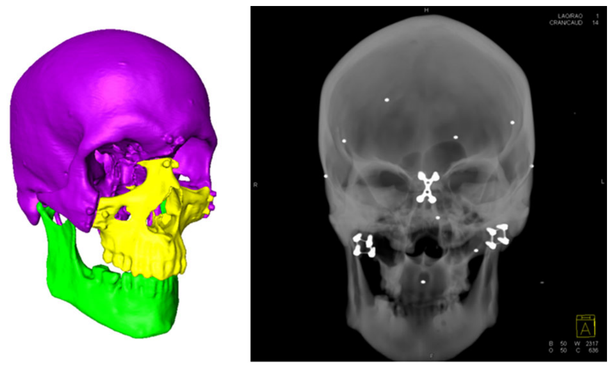

Fig. 8 Postoperative CT segmentation of the human plastic models (*left*) and reconstructed projection view with fiducials highlighted (*right*)

Postoperative CT scans at $0.45 \times 0.45 \times 0.60$ mm resolution were obtained and an automated threshold-based segmentation provided an initial labeled CT volume. Manual improvements separated the plastic models (Fig. 8). An automated, high-threshold segmentation identified the fiducials in the postoperative scan. Each fiducial was automatically identified in the CT volume as a series of connected voxels. The geometric center (average, unweighted position) of the voxels defined the center of each fiducial.

Two CT registration techniques identified the postoperative placement of the donor segment for the plastic model transplants: (1) fiducial-based registration and (2) volumetric-based registration; accuracy for the human cadaver test was measured through volumetric-based registration only. The fiducial-based registration procedure used a point-to-point registration technique [28] between the corresponding preoperative and postoperative fiducials. The volumetric-based registration employed a normalized mutual information (NMI) technique in Amira (Visualization Sciences Group, Burlington, MA, USA) to align the volumes. To ensure the best accuracy, the raw preoperative and postoperative CT data were masked with the volume labels to only compare analogous bony anatomy (e.g., the recipient cranium). Manual alignment initialized the NMI registration routine.

Three types of errors were measured in this study: (1) intraoperative to planned; (2) postoperative to planned; and (3) intraoperative to postoperative (navigation error). The intraoperative placement is measured through CT data, and the postoperative placement is measured as described above. The measured transformations were applied to the preoperative surface model of the maxilla to maintain a consistent model and coordinate frame for comparison. The distance error between corresponding vertices on the maxilla surface model was computed—there were 4,975 vertices in the swine plastic model, 4,939 in the human plastic model, and 7,412 in the human cadaver.

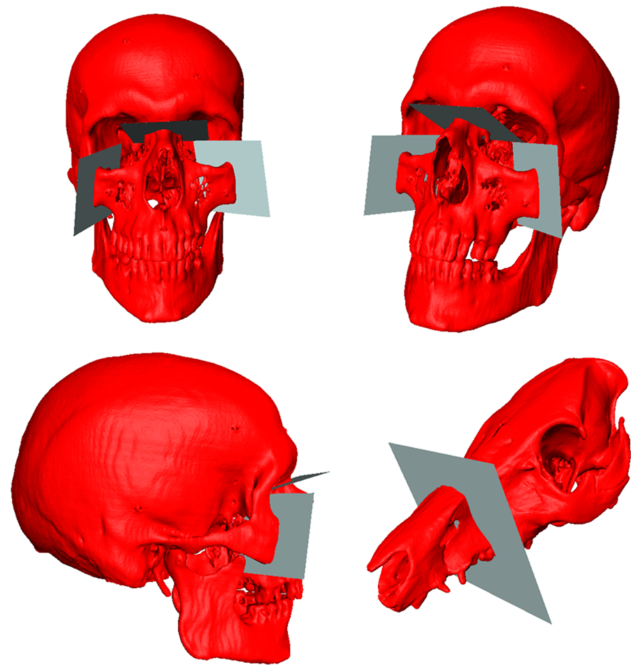

Fig. 9 The cut planes on the swine and human models

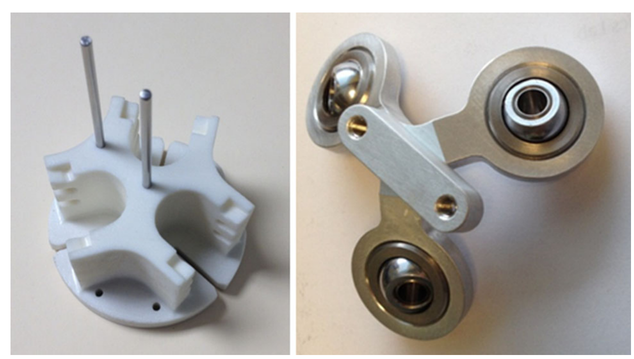

Fig. 10 Cranial reference attachment designed for swine (*left*) and redesigned version for human and swine anatomy (*right*)

Results

Due to significant (unpublished) practice with the CAPE system, we completed each mock surgery without complication. Moreover, the nature of the mock surgeries (no soft tissue, no bodily fluids, etc.) enabled improved access to the dentoskeletal anatomy of interest. During the procedures, we identified a few areas of improvement, including:

1. In the human scenario, attaching the donor fragment to the recipient is not as simple as in the swine operation. With swine, there is a single curve (cutting plane) along the bone, while for the human case, cuts are made in three separate plane locations (Fig. 9). The human approach, then, requires multiple fixation points along multiple planes. Several potential improvements exist for this problem, including an updated guide design, which "locks" the fragment in place by temporarily fixing the donor guide and recipient guide together.
2. The reference attachment originally designed for the swine's skull is not appropriate for the human skull. Specifically, the curvature of the human skull did not allow for full fixation of the reference hardware as planned. However, a new redesigned version functions on both swine and human, has a low profile and light-weight design, and will not disrupt the surgeon (Fig. 10).

The intraoperative model-to-patient registration routine for the CAPE system exhibited errors of 0.727 and 0.306 mm for the human plastic model donor and recipient, respectively. The errors on the human plastic models were comparable to those exhibited on swine—0.510 and 0.357 mm for swine donor and recipient, respectively. Human cadaveric testing showed registration errors of 1.22 and 0.745 mm for the donor and recipient, respectively.

The different postoperative registration techniques (fiducial-based and volumetric-based) showed similar error values (Table 3). As such, the volumetric-based registration errors are used for the remainder of the paper to enable comparison between tests with the plastic models and the human cadaver. Error analysis on the intraoperative placement of the donor fragment indicated reduced error on the swine compared with the human. The average navigation error (postoperative measurement compared to intraoperative measurement) for both plastic model tests did not exceed 1.250 mm

Table 3 Placement error for human and swine surgeries

	Intraop to planned	Registration type	Postop to planned	Postop to intraop
Human [plastic model]	2.62 ± 0.36	Fiducial	2.96 ± 0.53	1.23 ± 0.35
		Volume	2.91 ± 0.42	0.85 ± 0.28
Swine	2.68 ± 1.10	Fiducial	1.81 ± 0.77	1.20 ± 0.28
		Volume	2.25 ± 0.97	1.21 ± 0.32
Human [cadaver surgery]	3.29 ± 0.87	Volume	2.26 ± 0.18	3.59 ± 1.78

Errors are in mm, presented as mean ± SD

regardless of postoperative registration technique (Table 3). There was increased error in the final placement of the donor fragment with respect to the planned position for the human plastic model test case (2.91 mm) compared to the swine test case (2.25 mm); however, intraoperative accuracy between the plastic model tests was comparable. Human cadaver testing demonstrated increased navigation error (3.59 mm) compared to the plastic models, but the final placement error was 2.26 mm—lower than the human plastic model.

Each of the plastic model surgeries had the mandible (lower jaw) disconnected from the cranium. This makes postoperative occlusal evaluation difficult. However, results from the cadaver testing showed the postoperative hybrid occlusion matched the planned occlusion. The plan aligned the arches to provide a "reasonable occlusion" for this hybrid jaw in relation to arch alignment, occlusal plane, and tooth interdigitation, as estimated by the surgeon and periodontist. An open bite was planned on the posterior right, with posterior left contact, centered alignment of the central incisors, and minimal overbite/overjet (postoperatively measured to be less than 4 mm). The planned occlusion kept acceptable cephalometric measures with a sella–nasion–A point (SNA) angle of 81 degrees indicative of a normal maxillary-cranial relationship [29]. As noted by the fragment accuracy, the cuts were achieved and the postoperative results were qualitatively near the planned occlusion.

Discussion

The CAPE system was developed to improve outcomes in complex craniomaxillofacial procedures including Le Fort-based FJTT [19,20]. This paper presents a feasibility study of the navigation system by comparing measured intraoperative data with postoperative data. Moreover, this study reports on the accuracy with which we achieved a planned alignment of the donor face–jaw–teeth fragment onto the recipient utilizing a size-mismatched scenario in both swine and humans. This exhibited the capability of transitioning the CAPE system from swine (the basis of the initial development) to human anatomy without making changes to the system.

The results from this study exhibit the feasibility of intraoperative, navigated guide placement and real-time, fragment tracking. While results on the swine model reported higher (postoperative) positioning accuracy relative to the plan (2.25 mm as compared to 2.91 for the human plastic model), the accuracy relating the postoperative position and intraoperative position were comparable (1.21 mm as compared to 0.85 mm for the human model). The reported accuracy on the human model with no system changes bodes well for future applications of this system to FJTT and various procedures within craniofacial orthognathic surgery. Moreover, the final position of the donor maxilla fragment could not be measured since the guide must be detached before full fixation—this likely indicates improved overall accuracy from what this paper reports.

Cadaveric testing showed increased navigation error as compared to the plastic model surgeries. The main contributor to this is the increase in error of the donor and recipient registrations, an average of 0.98 mm for the cadaver test versus 0.48 mm for the plastic models. This is expected given the complexity of the cadaveric environment—soft tissue restrictions like rigor mortis, minimal bony exposure—as compared to plastic models. However, guide performance in the cadaveric environment (measured by the postoperative positioning error) was on par with the swine plastic model, and better than the human plastic model. While the advantage of navigating the guide placement cannot be established with this work, one can consider scenarios in which, because of the existence of the residuals of soft tissue over the bone surface, the navigated guide may end up improving the placement accuracy. More importantly, the trackable guide is notably useful as a dynamic reference for measuring real-time cephalometrics and allowing visual feedback during donor fragment placement onto the recipient

Compared to navigation systems for other surgeries (e.g., orthopedics), this system presents significant challenges. Orthopedic surgery has an advantage of large or (comparatively) thick bones used to fix reference devices. For this surgery, one is limited to the thickness of the skull; penetration of screws into the brain of either the donor or recipient would be a significant problem. As such, much smaller (about 4 mm threaded length and 2 mm diameter) screws fix the reference device on the parietal skull compared to at least

20 mm threaded length and 3 mm diameter screws used in optically navigated orthopedic surgery (e.g., Ortho Navigation, Medtronic, Minneapolis, MN, USA; Brainlab Image-Guide Surgery Systems, Munich, Germany; [30,31]). However, the reported registration accuracy matches that reported for surface-based registration in orthopedic surgery [31].

Some difficulties transitioning from swine surgery to human surgery were noted during the mock surgeries. One significant obstacle was the plate-screw fixation process of the donor fragment onto the recipient. One potential fix is an improved guide design that incorporates a locking mechanism for attaching the donor and recipient guides. This would allow the surgeon to partially fix the fragment using guides in the desired location, check the accuracy of the placement using the system, and fully fixate the fragment using rigid titanium plates. In addition, the initial reference designed for the swine skull did not translate well to human anatomy. The improved, lower-profile design of the new reference geometry further enables this translational research and updates the system for both types of environments (human and swine).

The integration of cutting guides and navigation potentially allows the CAPE system to achieve higher accuracy than either system independently. Recent literature [32] on a CAD/CAM system using non-navigated cutting guides report 7.18 mm error in predicted compared with actual placement of a Le Fort III-based maxilla and mandible transplantation. The results reported in this study comparing post-operative location to the plan (2.96 mm translational error for a Le Fort-based, single-jaw–teeth transplant for human) suggest significant improvement from a non-navigated cutting guide positioning and fragment transplant—and may therefore represent a major advancement in computer-assisted technologies applicable to orthognathic surgery. The cutting guides help the surgeon perform cuts at pre-defined locations and angles, which may not be achievable with as much accuracy using navigation alone.

The navigation system helps ensure that the cutting guides are placed appropriately, avoiding numerous sources of "surgeon-related" and "manufacturing-related" error. Previous research identified the potential for cutting guides to be positioned and secured with some small error; the navigation component can help the surgeon identify when that error occurs and correct the guide positioning [20]. Although the use of plastic models is a limitation for this study, the mock environment reduces many potential error sources and cofounding variables such as bleeding bone and inconsistent soft tissue contraction/relaxation. The accessibility of the entire plastic model allows the surgeon to digitize registration points at many locations; this may conflict with the reduced bony exposure in a clinical environment. However, these plastic models did allow the necessary position flexibility to assess the CAPE system accuracy (at various time points throughout the surgery) via frequent model manipulation—which would not be feasible in the cadaver or live surgery setting.

The materials used for the bone models in the plastic models were significantly more difficult to interact with as compared to real bone. For instance, the surgeon reported increased difficulty in attaching the guides and fixation plates since the self-drilling bone screws were less effective as compared to real bone. Additionally, the material used for printing the cutting guides had some mechanical flexibility. This flexibility is useful for accounting for minor differences in the CT segmentation and actual anatomy during surgery. However, the navigation system models this as a rigid guide and cannot accurately capture these small deviations.

The described technology in this work relies on the use of diagnostic CT information for preoperative planning. Cone-beam CT is an emerging technology in various applications including dental and head/neck surgery, which which also offers high resolution images. This increased resolution offers more information about the bone, but the poor contrast and high noise may be detrimental and will increase segmentation/planning time. Most cone-beam CTs of the head/neck require the patient to be seated upright—a challenging task to achieve with the donor.

Transitioning this system to clinical trials still requires a significant amount of testing. The human cadaver test showed that the presence of soft tissue in the CT scan does not hamper the segmentation, model reconstruction, or cutting guide design, but will impact the registration. Moreover, the cutting guide can be affixed with only the skin incisions required for the transplant. Some clinical donors or recipients may present with metallic fillings in teeth causing artifact in the CT volume. These artifacts will pose difficulty in truly predicting the hybrid occlusion resulting from the single-jaw–teeth transplant and will need to be addressed in future iterations on this work.

Planning routines for each surgery can likely be completed within 5 h per case. This includes segmentation, alignment of the donor CT to recipient, planning the cutting planes, and designing the patient-specific guides. The guides must be printed overnight, but this is a "set and forget" operation. While this may add additional time preoperatively, it can likely save time during the operation and lead to improved outcomes—a very appropriate tradeoff.

The tools and techniques developed with this system may provide a substantial benefit to more traditional orthognathic surgery, ENT surgery, neurosurgery, and head/neck surgery. For example, the features within the CAPE system —such as real-time cephalometry—may reduce or remove the time-intensive process of hand-molded acrylic splints or costly process of virtual occlusal splint fabrication for all orthognathic cases. The stable reference mounted on the parietal bone provides a rigid navigation frame that may allow surgeons to do away with conventional pinning techniques used to maintain skull rigidity (i.e., skull clamp), especially in instances where concomitant scalp reconstruction is required.

In conclusion, this study presents the feasibility and translation of the CAPE system for Le Fort-based face–jaw–teeth transplantation. This preliminary data suggest promising results further showing the feasibility of the system and showing full translational capabilities to human anatomy. Future work will focus on validation through human cadaver studies, and moving forward with live swine surgery for additional feature development and pre-clinical safety testing. The CAPE system offers surgeons a new path forward in achieving improved outcomes in craniomaxillofacial surgery including Le Fort-based, maxillofacial transplantation. Furthermore, these technological advancements may be carried over into other surgical areas including orthognathic surgery, ENT surgery, neurosurgery, and head/neck surgery.

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Conflict of interest The authors declare that they have no conflict of interest.

Ethical standard The manuscript does not contain clinical studies or patient data and an approval by an ethics committee was not applicable. All human cadaver specimens were donated and prepared in accordance with the bylaws presented by the Maryland State Anatomy Board.

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