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The View from Below

Transtracheal Miniendoscopic Visualization of the Trachea and the Glottis

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CLINICAL situations arise in which it is necessary to visualize the subglottic region, either to monitor the extent of disease or to confirm intratracheal placement of an airway device. In patients with abnormal laryngeal anatomy and a narrowed glottic opening, it may be difficult to pass a fiberoptic scope,[1] and a minitracheotomy is necessary to visualize the larynx from below.[2]

In patients who require an elective intratracheal surgical access procedure,[2] it is possible that the finder needle position tip is outside the trachea and that forcible insertion of the airway device into the neck could result in traumatic complications. An added measure of safety would be added to these procedures if intratracheal entry were to be visually demonstrated before insertion of the airway device.

We present the results of a pilot feasibility imaging study involving the use of a thin miniendoscope in 3 human cadavers and 10 dogs for the transtracheal examination of the glottis and the trachea. In the animal study, the device was also used to visually confirm intratracheal access before performance of a surgical airway procedure, either cricothyrotomy[3,4] or percutaneous tracheostomy.[2]

Materials and Methods

Subjects

With approval of the University of Southern California Institutional Review Board (Los Angeles, California), three adult human cadavers fixed with formalin were studied.

With approval of the University of Southern California Animal Care Committee and with veterinarian supervision, 10 mixed hounds (mean age, 1.3 yr; range, 1–3 yr; mean weight, 22 kg; range, 18–31 kg) were induced intravenously with acepromazine, sodium pentothal, atropine, and pancuronium. Standard monitors (electrocardiograph, noninvasive blood pressure, and pulse oximetry) were applied. Animals were intubated with an 8- to 9-mm-ID endotracheal tube (ETT), provided with 100% oxygen–isoflurane general anesthesia, and mechanically ventilated with a Narkomed Drager anesthesia machine (North American Drager, Telford, PA). At the end of the experiment, animals were euthanized with pentobarbital.

The Miniendoscope

Recent developments in endoscopic technology have allowed the creation of extremely thin miniendoscopes. Figure 1 shows a Karl Storz miniendoscope (Karl Storz Endoscopy, Tuttlingen, Germany) with a distal needle-shaped semirigid fiberoptic telescope (spanned by the two fingers), which is 1.2 mm in OD and 10 cm in length. The telescope has a 0° direction (straight-forward looking) and a 70° angular sector of visualization. The telescope is connected to a 30-cm-long fiberoptic cable that terminates in a remote eyepiece. A Xenon/Nova (Karl Storz Endoscopy) light source connects at the perpendicular adapter. For insertion through tissue, the distal telescope can be contained and advanced within a sharp-pointed sheath with an infusion port. In this study, the endoscopic image was viewed on a video monitor screen. Although the needle endoscope is thin enough to pass through an 18-gauge catheter, we chose to use a 14-gauge catheter for all animal procedures.

Methods

In three adult human cadavers, the endoscope was inserted through the cricothyroid membrane and was used to view the glottis from below (cephalad view) and to view the trachea from above (caudad view).

In 10 anesthetized intubated dogs, the 14-gauge intravenous needle-in-catheter was inserted either through the cricothyroid space (in 8 cases) or through a lower tracheal site (in 2 cases). Initial confirmation of intratracheal placement was with air aspiration into a saline-filled syringe. The needle was withdrawn, and the catheter was left in place. The thin miniendoscope was advanced through the catheter and was used to confirm intratracheal placement of the catheter tip. Intratracheal confirmation was verified by recognition of familiar structures, such as the vocal folds and anterior tracheal rings.

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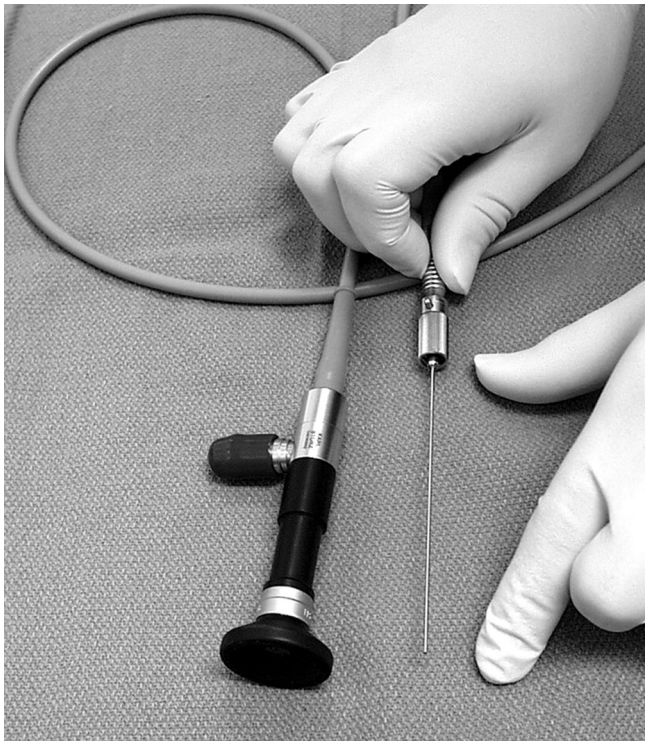

Fig. 1. A miniendoscope (Karl Storz Endoscopy), which is 1.2 mm in OD and 10 cm in length. The telescope has a 0° direction (straight-forward looking) and a 70° angular sector of visualization. It is connected to a light source and an eyepiece.

In eight dogs, a cricothyrotomy kit (Melker Emergency Cricothyrotomy Catheter Set; Cook Critical Care, Bloomington, IN) was used. In this technique, a wire guide is passed through an intratracheal catheter, the catheter is removed, and an enlarging scalpel incision is made. A tapered 12-French dilator is placed in a curved 4-mm-ID cannula and is advanced over the guide wire. The dilator and guide wire are removed, and the curved cannula is left in place.

In the two other dogs, a Blue Rhino percutaneous tracheostomy kit (Cook Critical Care) was used. The Blue Rhino is a curved, tapered dilator that creates, in a single pass, a tracheostomy opening. First, a guide wire is passed through an intratracheal catheter. After use of a small dilator, the Blue Rhino is passed over the guide wire to dilate the tracheal orifice. The Blue Rhino is removed, and a tracheostomy tube with an inner cannula is inserted. In this study, the two Blue Rhino procedures resulted in a low-lying tracheostomy several centimeters below the cricothyroid membrane.

Results

Adult Human Cadavers

In each of the three human cadavers, the miniendoscope was inserted through the cricothyroid membrane. The scope tip was steadily advanced through soft tissue until it entered the tracheal lumen. Confirmation of intratracheal placement was made through the identification of anterior tracheal rings. With the scope pointed downward (caudad), the tracheal rings were readily seen. When the scope was pointed upward (cephalad), the glottic opening could be seen, and it was readily possible to pass the needle-sized endoscope through the triangular-shaped vocal cords. In figure 2, the three pairs of cadaver images are shown.

Dogs

Anatomically, the dog larynx differs from the human one in that the dog has a barking structure, referred to as a vestibular fold, which sits inside the vocal folds. The triangular shape of the vocal folds, containing the inner vestibular folds, were clearly distinguishable (fig. 3, *first row*).

With the scope positioned facing the glottic opening, one could visualize the vocal folds and then advance the ETT forward through them, in a controlled reenactment of an actual intubation, (fig. 3, *second row*) or conversely and then back through the folds, as in an extubation. By keeping the scope fixed in position, it was possible to guide the scope directly into the lumen of the ETT, in effect achieving the equivalent of a subglottic retrograde intubation. The scope tip could also be maneuvered alongside the ETT in the immediate proximity of the vocal cords.

With cephalad positioning of the miniendoscope, the tracheal lumen and its anterior rings could be identified consistently (fig. 3, *third row, left*). In one dog, with the miniendoscope directed caudad, a Univent tube (Fuji Systems, Tokyo, Japan) was advanced under direct visualization into the left mainstem bronchus for one-lung ventilation. Finally, with conventional laryngoscopic visualization, one could see the lighted end of the fiberoptic scope protruding through the vocal cords (fig. 3, *third row, right*).

Discussion

The current pilot study indicates that subglottic visualization with a thin miniendoscope is readily possible. The major potential applications for such a miniendoscope include (1) diagnostic purposes (*e.g.*, examination of the vocal cords and the trachea in patients with laryngeal cancer, burns, or prolonged ETT placement) and (2) performance of elective airway procedures (*e.g.*, retrograde intubation,[5,6] elective percutaneous tracheostomy[2]).

Difficulties in using the instrument were related primarily to the fiberoptic scope being a semirigid structure. To achieve a better view of the glottis, the scope often had to be flattened, *i.e.*, it had to be placed almost parallel to the neck. This often required repositioning of the catheter, followed by the fiberoptic scope. A common error was to insert the catheter too far so that its tip

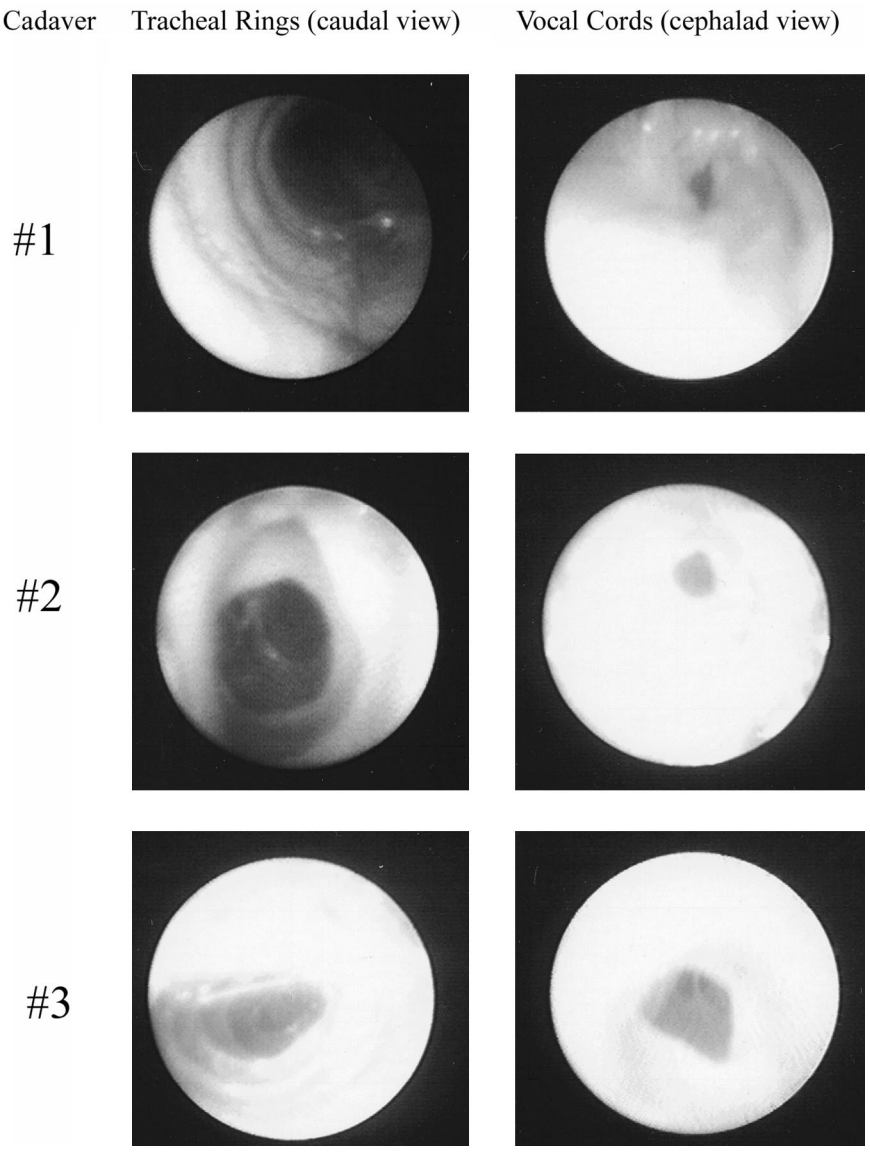

Fig. 2. In three human cadavers, the miniendoscope was inserted through the cricothyroid membrane and into the trachea. Confirmation of intratracheal placement was made through the identification of tracheal rings. When the scope was pointed downward (caudad), tracheal rings were readily seen. With the scope pointed upward (cephalad), vocal cords could be seen, and it was possible to manually advance the needle-sized endoscope through the triangular-shaped vocal cords.

was close to the opposite tracheal wall, which in turn limited the length of scope that could be introduced into the trachea. Depending on the position of the scope, a helpful maneuver at times was the manual lifting of the trachea. In three dogs, a small amount of heme was noted, which initially obscured the view. However, syringe flushing with a few milliliters of saline readily cleared the field.

The current needle-shaped design for the miniendoscope is not optimal for subglottic visualization. Ideally, the shaft of the endoscope should be curved so that, on entering the tracheal interior, it is less likely to encounter the opposite tracheal wall and can be better directed either cephalad (even beyond the cords) or caudad. If the miniscope were extendable in length, it could be used as a lighted stylet for a retrograde intubation.[5,6] With a longer and better designed scope, which either serves as the guiding stylet itself or which encompasses a guide wire, visually guided retrograde intubation would be quite easy. Alternatively, the scope could function as a distal guiding light to direct the laryngoscopist in an attempted conventional intubation.

If time permitted and no major bleeding was present, an added measure of safety might be added to emergency airway procedures—transtracheal jet ventilation,[7,8] cricothyrotomy,[3,4] and retrograde intubation[5,6]—if the needle endoscope was visually demonstrated to have its tip inside the trachea (1) before the jet ventilator was activated, (2) before the cricothyrotomy catheter was forcibly inserted over a stylet through tissue, and (3) before the retrograde wire was advanced through the needle in the cricothyroid space.

In the absence of visual confirmation, it is possible that, with blind advancement, the tracking needle tip may not end up inside the trachea, but rather outside the trachea within the neck. By using the needle endoscope to visually confirm intratracheal placement before insertion of the larger and thicker airway access device, it

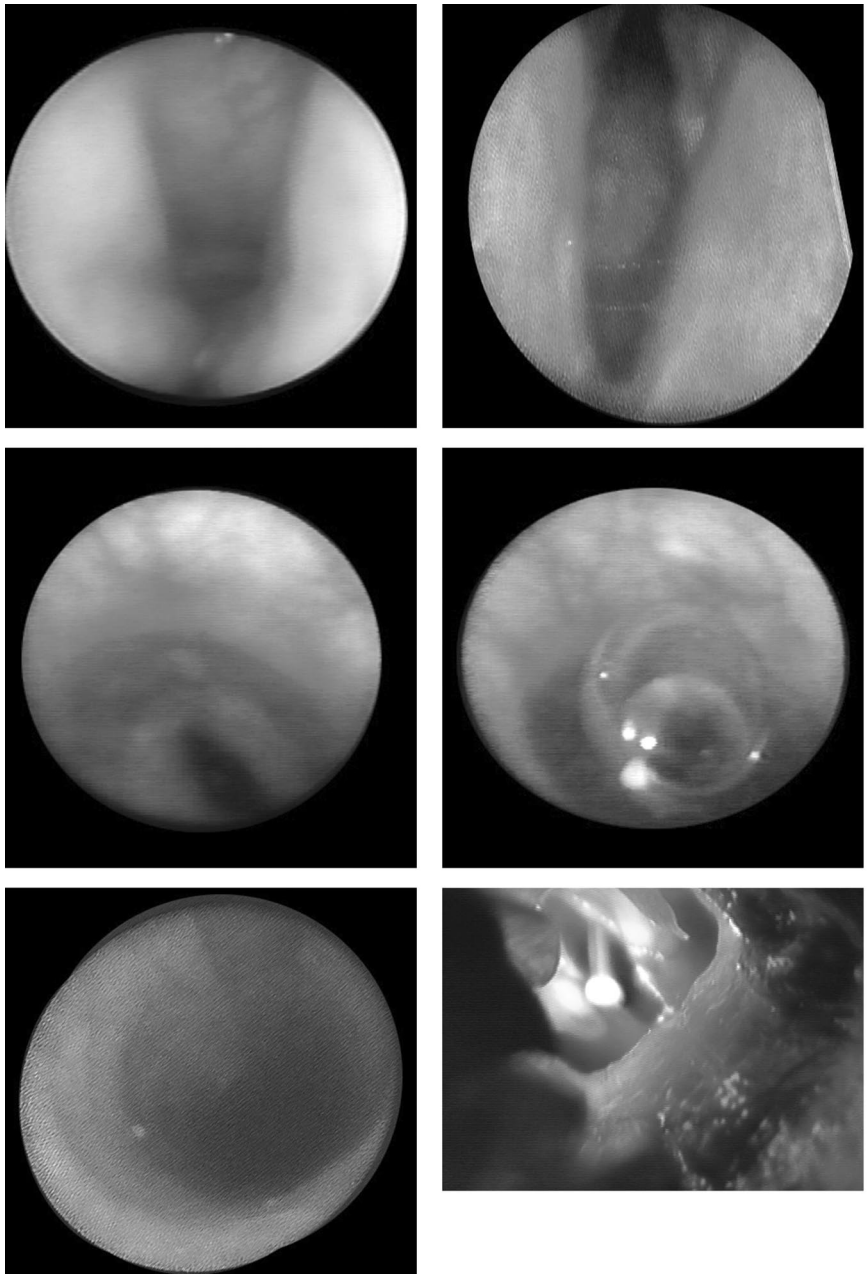

Fig. 3. (*First row*) Subglottic views of canine vocal folds. Note the inner vestibular (barking) folds. (*Second row*) (*Left*) Canine vocal folds seen from within the trachea. (*Right*) A few seconds later, advancement of the endotracheal tube through the same canine vocal folds under direct miniendoscope visualization. (*Third row*) (*Left*) Tracheal rings in the canine trachea (caudad view). (*Right*) The lighted end of the miniendoscope protrudes through the canine vocal folds (laryngoscopic view).

seems that the risk of device misplacement would be reduced. This, in turn, would lead to a reduced incidence of traumatic complications (subcutaneous or mediastinal emphysema of the neck with a jet ventilator, hematoma from vessel injury, esophageal perforation, thyroid damage, and pulmonary barotrauma). Even if the needle-shaped endoscope were to be advanced incorrectly into a key neck structure, the extent of the damage would be far less than that associated with the larger airway devices.

Because the clinical occasion for the use of these airway devices is rare, many practitioners, especially those unfamiliar with emergency airway care, are ill at ease with the use of these devices, and they are often hindered by the knowledge that device misplacement in the neck could lead to significant complications.[9] It seems that these individuals would be more inclined to use such a device if it were able to provide visual evidence of proper insertion.

In summary, a thin miniendoscope can be used to visually confirm intratracheal access. We believe that further studies will reveal that this type of miniendoscope can be used for diagnostic, therapeutic, and procedural purposes in the subglottic airway.

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Genetic Variability of μ-Opioid Receptor in an Obstetric Population

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INTERINDIVIDUAL variability in pain perception and sensitivity to analgesic therapy has been long noted. Although opioids are among the most widely used drugs for the management of acute and chronic pain, they display large interindividual variability in efficacy, side effects, and tolerance profiles. The μ-opioid receptor (μOR), which is encoded by genetic locus *OPRM1*, has been the focus of numerous genetic studies[1–5] because this receptor is the primary site of action for many endogenous opioid peptides, including β endorphin and enkephalin, and the major target for opioid analgesics, such as morphine, heroin, fentanyl, and methadone. The μOR is a G protein–coupled receptor, and a number of single-nucleotide polymorphisms (SNPs) have been described for *OPRM1*.[6–10] At nucleotide position 118, an adenine substitution by a guanine (A118G) resulting in the asparagine residue at amino acid position 40 changed into an aspartate residue (Asn40Asp) has been reported to occur at an allelic frequency of 10–20%.[7,11,12] *In vitro*, the A118G polymorphism seems to increase the binding affinity and potency of β endorphin.[11] Therefore, individuals carrying the variant receptor gene may show differences in some of the functions mediated by β endorphin action at the altered μOR.[11]

The A118G polymorphism has not been studied in relation to postoperative or labor analgesic requirements. The purpose of this study was to determine the allelic frequency of the G118 variant in our obstetric population because a high prevalence of the G118 allele suggests that it could contribute to the known heterogeneity in pain perception, pain threshold, and opioid responsiveness.

Materials and Methods

Subjects

The study protocol was approved by the Institutional Review Boards of Geneva and Columbia University Medical Centers, and subjects gave written informed consent. Subjects were 181 women who gave birth at the Geneva University Hospital (Geneva, Switzerland) or Columbia University Medical Center (New York, New York) between October 2001 and April 2003 and consented to give blood for DNA analysis. Genotyping for the A118G μOR polymorphism was performed as described below. One hundred thirty-seven women from Geneva and 44 women from New York were genotyped. All subjects were healthy parturients with uncomplicated pregnancies and deliveries at term (> 37 weeks' gestation) with no clinically significant abnormality shown by routine history, physical examination, or laboratory test results. Women with a known history of drug abuse were excluded.

Genetic Analysis

DNA Collection. Peripheral blood was collected in 10-ml EDTA tubes from selected subjects. DNA was purified by a nonphenolic method using a Puregene Blood extraction Kit (Gentra, Minneapolis, MN) and tested for molecular weight on gel electrophoresis and purity quality by optical densitometry measure (260/280 nm).

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SNP Genotyping.

All genotyping was performed at the University of Geneva. For identification of A118G (N40D) in gene *OPRM1*, 60 ng DNA from subjects was amplified by polymerase chain reaction under standard conditions using the annealing primers forward (5' end-labeled with biotin) 5'- CCGGCCGTCAGTACCAT-3' and reward reverse 5'-GTAGAGGGCCATGATCGTGAT-3'. Polymorphism A118G (GATGGCRACCTGT) was then genotyped on the 247-bp polymerase chain reaction fragment by a minisequencing method§ using sequencing (reward reverse) primer 5'-TGGGTCGGACAGGT-3' as follows.

Polymerase chain reaction products were immobilized with Dynabeads (Dynal, Oslo, Norway) by a 15-min, 65°C incubation in a buffer containing 10 mM Tris-HCl, 2 M NaCl, 1 mM EDTA, and 0.1% Tween 20. Polymerase chain reaction products were then removed from solution using magnetic separation, denatured with NaOH 0.5 M, and washed with 200 mM Tris-Acetate, 50 mM $MgAc_2$. The remaining single-stranded DNA was then hybridized with the internal "sequencing" primer by heating the mix to 80°C and slowly cooling it to room temperature. Next, enzyme and substrate mixes were automatically added to each well, and the reactions were processed at 28°C by the sequential addition of single nucleotides with a predetermined order. Luciferase peak heights were proportional to the number of nucleotide incorporations, which have been shown to possess a high degree of correlation (5% error rate) in a number of experimental settings.[13,14]

Statistical Analysis

Proportions of genotypes for *OPRM1* are expressed as percentage of total (95% confidence interval). The allele frequencies were calculated using the gene-counting method. The significance of differences in allele and genotype distribution in the two populations, as well as demographic data, was determined using the chi-square or the Fisher exact test, with $P < 0.05$ being the minimal value accepted as statistically significant.

Results

Self-reported racial distribution and demographic data were similar at both institutions (table 1). Genetic distribution was similar with regard to race and when compared between institutions (table 2). Overall, 121 women were A118 homozygous (67%; 95% confidence interval, 58–73%), 52 were heterozygous (29%; 95% confidence interval, 23–38%), and 8 were G118 homozygous (4%; 95% confidence interval, 2–9%). The overall allelic frequencies using the gene-counting method were 81.2% A118 and 18.8% G118.

§ Pyrosequencing. Uppsala, Sweden. Available at: http://www.pyrosequencing.com. Accessed December 12, 2003.

Table 1. Demographic Data

	HUG (n = 137)	Columbia, New York (n = 44)	*P* Value
Maternal age, yr	30 ± 6	30 ± 5	NS
Race			
White (n = 114)	84 (61%)	30 (68%)	NS
Hispanic (n = 67)	53 (39%)	14 (32%)	NS
Prepregnancy weight, kg	65 ± 14	67 ± 14	NS
Height, cm	162 ± 7	160 ± 6	NS

Data are presented as mean ± SD or percent.

HUG = Hôpitaux Universitaires de Genève; NS = not statistically significant, $P > 0.05$.

Discussion

Single-nucleotide polymorphisms are naturally occurring variants in the structure of genes that may have a significant influence on the metabolism, clinical effectiveness, and side effect profiles of therapeutically important drugs. Ethnic differences in drug response are in part genetically determined, but genotyping of individuals has significantly greater potential to improve the pharmacotherapy of disease (and pain). As the occurrence and function of genetic variants of drug targets become better understood, this knowledge should lead to the design and use of specific drugs or dosages in patients with differing genotypes.

We report a relatively high frequency of the A118G variant in a diverse obstetric population from two different institutions; our overall G118 allelic frequency was 18.8%. Because race has been shown to affect genetic variability, we compared the genetic distribution between institutions and between the two prevalent racial groups, namely white and Hispanic, and found no difference. Among whites, Bond *et al.*[11] reported that the expected frequencies of homozygous G118 and heterozygous subjects are 2% and 20%, respectively, with an 11.5% G118 allelic frequency, regardless of sex. Overall, among 150 African-American, white, and Hispanic subjects, the G118 allelic frequency was 10.5%. In Asian populations, genotype distributions of several μOR SNPs frequencies have been recently reported, with a G118

Table 2. μOR Genotype Distribution: Comparison between the Two Races and Two Institutions

	A118 (n = 121)	A118G (n = 52)	G118 (n = 8)
Race			
White (n = 114)	78 (68%)	31 (27%)	5 (4%)
Hispanic (n = 67)*	43 (64%)	21 (31%)	3 (4%)
Institution			
HUG (n = 137)	89 (65%)	42 (31%)	6 (4%)
Columbia, New York (n = 44)†	32 (72%)	10 (23%)	2 (5%)

* Chi-square test; $P = 0.83$, not statistically significant. † Chi-square test; $P = 0.57$, not statistically significant.

HUG = Hôpitaux Universitaires de Genève; OR = opioid receptor.

frequency in control subjects ranging between 35 and to 47% (Chinese, 35%; Thai, 44%; Malay, 45%; Indian, 47%),[15] and the reported frequency among Japanese is 49%.[12] Interestingly, a recent study from California studying a group of 109 subjects (61% white) did not find any subjects with the G118 allele.[16]

Alterations of the encoded receptor may have functional consequences for receptor activity such as binding affinity and potency. Bond *et al.*[11] demonstrated a threefold increase in binding affinity and potency of β endorphins at the G118 variant of the μOR *in vitro*. The A118G variant predicts an Asn to Asp change at amino acid 40 of the receptor. Because the Asn residue is a putative site for N-glycosylation at the N-terminal region of the μOR, this variant may interfere with subsequent receptor glycosylation and alter agonist binding or activity. One possible mechanism of the pharmacologic differences between the genetic variants might be that the binding affinity of ligands to the variant receptor may be dependent on the size of the opioid ligand. Bond *et al.*[11] found that for most small opioid ligands, there was no change in binding affinity with A118G polymorphism, but there was a significant increase in binding affinity for the larger endogenous opioid peptides, such as β endorphin. Furthermore, β endorphin seemed to be three times more potent at the altered μOR. These findings, however, have not been consistently demonstrated. Befort *et al.*[17] found that although an extremely rare SNP in the third transmembrane domain with a proline substitution for a serine (S268P) severely impaired receptor signaling, the A118G variant did not modify the functional properties of the receptor.

In vivo, the influence of the A118G polymorphism on the clinical response to morphine and morphine-6-glucuronide (M6G), an active metabolite of morphine, has been evaluated.[18] Pupillary constriction, a measure of the central effects of opioids, was reduced in subjects with A118G variant after the administration of M6G but not morphine. These same authors sought to investigate the risk for M6G accumulation and opioid overdose and toxicity in two patients with severe kidney failure genotyped for SNPs of the μOR.[19] One patient tolerated morphine treatment despite high plasma M6G and was found to be homozygous for the G118 allele. The other patient, homozygous for the wild-type allele A118, was found to have severely impaired vigilance during the first day of morphine treatment. The authors postulated that the G118 allele may be one of several genes or factors conferring protection against M6G-related opioid side effects and perhaps toxicity. Recently, two studies have reported that individuals with a G118 allele (five heterozygotes, one homozygote) had an increased cortisol response to the administration of naloxone compared with A118 homozygotes, suggesting that there may indeed be clinical consequences to this polymorphism.[20,21]

There is evidence for a key role for the opioid system in the pathophysiology of substance abuse[22,23]; therefore, the μOR is an ideal candidate gene for susceptibility or protection from addictive behaviors. Nonetheless, studies on the association of the A118G variant with alcohol dependence or drug abuse have not been consistent. Bond *et al.*[11] reported that the A118 allele was present in a significantly higher proportion of opioid-dependent Hispanic individuals than non–opioid-dependent individuals. An association between the A118 allele and alcohol dependence among white alcoholics was also reported,[24] but this finding was not confirmed by others.[12,25–27] Another study in white subjects abusing alcohol, cigarettes, cocaine, marijuana, or other illegal drugs found that there was a significant association between substance dependence and the A118 allele.[28] Interestingly, the response to naltrexone, a μOR antagonist used for treatment of alcohol and opioid dependence, has been shown to be significantly better among white alcoholics carrying the G118 allele, with significantly lower rates of relapse and a longer time to return to heavy drinking, than alcoholics homozygous for the A118 allele.[29]

The most commonly used approach for the study of "pain genes" is gene expression assays relying on previously identified genes or complementary DNA sequences of interest. Despite great advances in transgenic technology and genetic mapping of selected candidate genes, we are far from having elucidated the genetics of pain. Studies of the μOR gene may provide insight into the mechanisms involved in the interindividual differences in physiologic responses to endogenous opioids, pain perception, and pain thresholds. Specific SNPs of the μOR may alter the response to opioids and also influence side effects, toxicity, and tolerance profiles. Information on μOR genotype may enable us to predict the response to μOR manipulation and allow opioid analgesic regimens to be tailored to individuals' genetic makeups. This should result in better pain management with fewer or milder side effects for labor and delivery, postoperative care, and chronic pain states. In the future, gene therapy of the μOR could be used for patients with chronic pain who are refractory to opioids. In addition, identifying SNPs relevant to opioid analgesia is likely to contribute to a better understanding of clinical conditions beyond analgesia, such as immune modulation, opioid reward mechanisms, and drug abuse.

To date, a handful of mutations/polymorphisms affecting pain in humans have been investigated. In our study, we found that a genetic variant of the μOR associated with an increased response to β endorphin is present in more than 30% of our obstetric population. Further studies investigating the clinical implications of this finding, such as the impact of this genetic variant on labor pain and neuraxial opioid requirements for labor analgesia, will be of interest.

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