10-19-2009

Capillary Blood Gas Measurement as a Novel Means of Assessing Flap Perfusion in Free Tissue Transfer

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A Thesis Submitted to the
Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

by

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2009

CAPILLARY BLOOD GAS MEASUREMENT AS A NOVEL MEANS OF ASSESSING FLAP PERFUSION IN FREE TISSUE TRANSFER.

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To demonstrate that in comparison to implantable O_2 microelectrodes, Capillary Blood Gas measurements represent a reliable, accessible and easy method of identifying failing free flaps, and furthermore, to assess post-operative free-flap monitoring techniques nation-wide, determining the openness of surgeons to new surveillance modalities.

Groin fasciocutaneous flaps were elevated in 10 rats and following arterial or venous occlusion, oxygen microelectrode measurements (pO_2 and flow) and Capillary Blood Gas measurements (pO_2, pCO_2, pH, HCO_3) were obtained at 0, 10 and 20 minutes. A nine question, Internet based survey on post-operative flap surveillance techniques was sent to the personal email addresses of 238 microvascular surgeons from around the country. Response data were collected and analyzed utilizing an online resource.

Measurements with capillary blood gas paralleled measurements with O_2 microelectrodes. Average capillary blood gas pO_2 fell from 42.72 mm Hg at 10 minutes and then to 28.67 mm Hg at 20 minutes. Average pH fell from 7.38 to 7.33 at 10 minutes and to 7.30 at 20 minutes. Results were statistically significant with both the paired Student's *t* test and the Wilcoxon signed rank test. 75% of survey respondents indicated that clinical assessment was more important than available adjunctive tests in the decision to re-explore the vascular pedicle in a threatened free flap and 56% listed pinprick with flap bleeding as an important marker of flap health in their practice. 90% of respondents indicated they are open to new quantitative monitoring techniques.

While providing users the ability to simultaneously monitor accepted modalities of flap surveillance, pH and pO_2, the capillary blood gas is a reliable and reproducible marker of flap tissue health. Given that no single monitoring modality enjoys a clear preference among microvascular surgeons and that more than half of these surgeons already utilize pinprick assessment of the flap, this study demonstrates that the capillary blood gas may be well positioned for further study in humans.

ACKNOWLEDGEMENTS

This thesis would not have been possible if not for the support and counsel of Dr. Douglas Ross. His initial encouragement to further explore the field of otolaryngology and to engage in a research project early during my time at Yale Medical School was highly influential in my residency decision. His wife, Dr. Ann Ross is to be credited with the initial idea of using the capillary blood gas as a monitoring technique in free flaps.

Dr. Gregory Lesnik, an otolaryngology resident, helped teach me the skills of microvascular surgery and tirelessly helped troubleshoot the laboratory portions of this project. Dr. Peter Herman deserves thanks as a wonderful resource in the neurophysiology lab where our experiments took place, as does the nursing staff of the Yale New Haven neonatal intensive care unit who taught me how to collect and quickly analyze capillary blood gas samples using portable equipment. All physician contact information used in the National Survey of Free Flap Monitoring Technique was obtained with the help of Chris Ubinger of Medtronic Corporation and to him I am thankful.

Dr. Richard Gusberg of Vascular Surgery and Dr. David Paltiel of the Yale School of Epidemiology and Public Health have served as wonderful mentors and deserve thanks for meeting with me on short notice and playing the realist in my thesis ambitions.

And last, I have to sincerely acknowledge the outstanding leadership, mentorship and counsel that Dr. Clarence Sasaki has provided. Since I first became interested in head and neck surgery he has encouraged my exploration and offered unparalleled support.

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INTRODUCTION

Any patient receiving a diagnosis of cancer in the head and neck will be rightfully distraught about the implications of their disease and its treatment. Composing ~3% of all newly diagnosed cancer each year,(1) head and neck malignancies are most often squamous cell carcinomas arising in the oral cavity, pharynx, larynx, nasopharynx or on the scalp. Curative treatment for these cancers relies on surgery, radiation or chemotherapy or some combination of the three, and while survival data is good relative to other cancers, there remains significant room for improvement. In treatment of moderate to advanced cancer, one major modality of therapy involves surgical removal of the tumor and reconstruction of the head and neck defect with a tissue autograph. Since a successful outcome depends on the health of the transplanted tissue and its vascular supply, detecting early warning signs of flap failure is of utmost importance. Flaps with compromise at their vascular pedicle can be returned to the operating room for repair of the artery or vein if found early in the course of arterial ischemia or venous congestion. Accordingly, postoperative monitoring of the graft is of central importance. This thesis will report on the validation and application of a novel method of free flap autograph monitoring.

Epidemiology and Etiology of Head and Neck Cancer

In the United States in 2008 it is estimated that 35,310 men and women will be diagnosed with cancer of the oral cavity/pharynx and 12,250 men and women will be diagnosed with laryngeal cancer.(1) Men are diagnosed at a rate three times as frequent as women, although year over year trends suggest that this gap is narrowing. For patients carrying a

diagnosis of squamous cell carcinoma of the larynx, oral cavity and pharynx, 11,350 will die from their disease in 2008.(1) Mortality data is nearly identical among black and white women, but mean survival time has been found to be markedly shorter in black men when compared to white men.(2) Fortunately, annual incidence trends in head and neck cancer are on the decline with decade length period changes between -1% and -2.7% from the 1970s to 2005.(1)

Head and neck cancers occur along the aero-digestive tract and squamous cell carcinoma is highly correlated with the abuse of alcohol and tobacco.(3) In recent years, public health efforts to curb tobacco use appear to have led to a decline in the overall rates of laryngeal, oral cavity and pharyngeal cancers(1); however, given the demographics of our aging population and their history of exposure to these carcinogens, the health care burden of these patients is likely not to change in the next two decades. Human papilloma virus (HPV) has is also associated with head and neck cancer, with 95% of cervical squamous cell carcinomas linked to persistent HPV infection.(4) While our understanding of this relationship is not completely clear, it appears that HPV infection may play a role as a carcinogen in a subset of head and neck cancer patients.

Presentation of Head and Neck Cancer

Cancers of the head and neck may go unnoticed or unappreciated at early stages because patients can present with a constellation of symptoms seemingly unrelated to serious disease. A detailed history and examination can properly identify the primary tumor in 95-97% of cases.(5) Patient complaints can be stereotyped by location as indicated below -

- Oral Cavity – Patients may complain of non-healing ulcers or persistent masses of the tongue, lip, buccal mucosa, floor of mouth, hard palate, alveolar ridge or retromolar trigone. Because of the rich lymphatic drainage to the oral cavity, these patients may also present with a mobile neck mass, usually ipsilateral to the lesion.
- Oropharynx and Supraglottic Larynx - Because these lesions arise in areas with little direct sensory innervation, presenting symptoms of cancers here include general dysphagia or odynophagia. Patients may also complain of otalgia due to referred pain via Arnold's or Jacobson's branch of the glossopharyngeal or vagus nerves, respectively. Cervical adenopathy is also an extremely common presenting sign in these patients as this area is drained bilaterally by a rich plexus of lymphatics.
- Larynx – Classically, patients will present with hoarseness or a change in voice quality. Patients with more advanced disease may have stridor, hemoptysis or chronic cough.
- Nasopharynx and Paranasal Sinus – Unilateral serous otitis media in an adult raises concern for Eustachian tube blockade, possibly by a tumor, but these patients may also present with a neck mass as their first sign of disease. Patients with paranasal carcinoma often complain of nasal obstruction or epistaxis.

Cost of Head and Neck Cancer

According to recent findings in a Surveillance Epidemiology and End Result (SEER)-Medicare retrospective analysis, patients with squamous cell carcinoma of the head and neck accrue large medical bills – 25,500 dollars per year more than the costs of a matched control without head and neck cancer.(6) These costs are reflective of the

complexity of their care, which involves head and neck surgeons, radiation oncologists and medical oncologists as well as inpatient and outpatient ancillary staff. Given that the cost of treatment increases with increasing stage of disease, (primarily due to a difference in relapse rates),(7) there are not only benefits in disease outcome, but also financial incentives in diagnosing and treating head and neck cancer at an earlier stage. Several large-scale primary care screening programs for head and neck cancer have been studied in Britain through the National Institute for Health and Clinical Excellence (NICE) and they have suggested a greater need for high-risk opportunistic screening by general dental and medical practitioners.(8) However, it has been found that there is no cost-effective role for imaging in the screening of primary lesions in the head and neck, even in high-risk populations.(9)

Treatment in Head and Neck Cancer

Treatment for head and neck cancer patients is often long, complex and costly.(6, 10, 11) Workup and treatment planning are frequently undertaken by a multidisciplinary tumor board that includes surgical, radiation and medical oncologists. Head and neck cancer is based on the AJCC's TNM staging scale and is correlated with tumor size, location of origin and involvement of surrounding structures. (Appendix 1)(12)

Patients presenting with early/localized staged disease and treated with either surgery or radiation alone enjoy five year survival rates of 62.5 percent to 99 percent, depending on tumor site and biological factors.(1, 13) However, more than fifty percent of all head and neck cancer patients present with locally advanced disease (stage III or IV) and necessitate more aggressive treatment.(1) Several randomized trials report that

these patients, whether receiving primary surgery followed by radiotherapy or induction chemotherapy followed by radiation, have five-year survival rates of 40 percent to 50 percent.(14, 15) Because outcome data for primary radiation versus primary surgery have paralleled each other for the past two decades, large regional variations in treatment protocols exist in the United States.(10, 16) At this institution, locally advanced disease may be treated primarily with aggressive surgical intervention, and when necessary, free flap repair. Surgical treatment is also utilized as salvage therapy in patients who fail primary radiation.

Reconstruction in Head and Neck Cancer

Reconstructing surgical defects following head and neck oncological resections is a great challenge. This difficulty stems largely from the lack of locally available tissues and/or the presence of surrounding irradiated tissues. Any irradiated tissues used in reconstruction have a higher failure and fistula rate than normal.(17, 18) Thus, in order to maximize the oncological benefits of surgery, reconstruction needs to be achieved quickly so that patients may go on to receive adjuvant therapies as soon as possible. For these reasons, free tissue transfer remains the best reconstructive option for many patients with head and neck cancer.

The use of free tissue flaps in head and neck reconstruction has expanded the opportunities for surgical resection and they are indispensable treatment options today for patients with advanced disease. Free tissue flaps have been described from over 20 donor sites and may include everything from skin and subcutaneous fat to muscle and bone.(19) The most frequently utilized flaps are the radial forearm fasciocutaneous flap, the rectus

muscular flap, the anteriolateral thigh muscle flap, the fibular bone and cutaneous flap and the scapular bone and muscular flap. Each of these volumes of tissue is harvested in a way to preserve its implicit vasculature and to minimize damage to tissues surrounding the donor site. Each flap is inset at the site of the oncologic resection and its vasculature anastomosed via microsurgery to a local artery and vein. The donor site is then covered with a local closure or by a split thickness skin graft taken most often from the thigh.

Flap Monitoring in Head and Neck Cancer

Despite technological advances in surgery, free tissue transfer maintains a failure rate of approximately 2 percent to 5 percent. (20, 21) Most commonly, free tissue transfer failures result from impaired arterial or venous flow, localized to the anastomosis. Ischemic times of greater than 6 hours results in irreversible tissue damage due to a "no-reflow" phenomenon. (22-24) In a no-reflow condition, the ischemic damage of worry is not the tissue parenchyma but the vascular network which itself collapses, thus preventing the proper return of blood from the ischemic tissue. For free flaps, the vascular compromise must be discovered within this narrow time frame. If this is the case, flap salvage is an option with success rates ranging from 69 percent to 95 percent. (20, 25, 26)

Clinical assessment as defined in the literature in free flap monitoring relates to the observation of color, capillary refill, skin turgor, tissue edema.(27) Because clinical assessment remains the gold standard in postoperative flap monitoring, numerous devices recording the metabolic microenvironment (also known as 'objective' or 'adjunctive' monitoring techniques) have been proposed to aid in identifying previously undetected

failed flaps. These include implantable Doppler flow systems, laser Doppler flow monitors, implantable oxygen tension monitors, implantable pH probes, and even implantable microdialysis catheters.(28-35) Because tissue oxygen tension is accepted as a sensitive and reliable method of determining adequacy of perfusion, researchers, since the 1980's, have helped to develop implantable microelectrodes that may be introduced into tissue to provide an instantaneous and constant measure of the oxygen availability.(31, 36-40) Impairing arterial or venous perfusion in experimental models has demonstrated a decline in the pO_2 and flow as measured with these devices.(31, 37) In humans, implantable microelectrodes have been used to appropriately identify and salvage free flaps with impaired perfusion,(32) but due to high cost and detailed operator training, these instruments have not been widely adopted.(31)

Oxygenation in tissues is directly related to oxygen levels in arterial blood. In humans, the gold standard for determining oxygenation and acid/base status remains the arterial blood gas (ABG). Repeated arterial puncture, however can lead to complications including pain, arterial injury, thrombosis with resultant distal limb ischemia and hemorrhage.(41, 42) Capillary blood gas (CBG) sampling is an alternate easy and inexpensive means of measuring acid/base status with diminished risk. CBG has been extensively studied in the pediatric/neonatal population as a less invasive determinant of respiratory status where ABG risks are greater. Researchers have found a significant correlation in pH, pCO_2 and pO_2 among ABG, venous blood gas (VBG) and CBG measurements, and as a result a host of studies in the pediatric literature confirm the validity of CBG in determining pH and pCO_2 status of critically ill children.(43, 44)

This thesis seeks to validate the capillary blood gas as a predictive monitor of the metabolic microenvironment of the postoperative free flap and to determine whether microvascular surgeons nationwide would be able and willing to supplement their current protocols with a more objective monitoring technique.

STATEMENT OF PURPOSE AND SPECIFIC AIMS OF THE THESIS

By transferring the application of capillary blood gas from a generalized determinant of oxygenation and acid/base status to a focused measurement of the metabolic micro-environment, our objective in this study was to show that the capillary blood gas may represent an easy to use and reliable new method of identifying failing flaps secondary to venous occlusion, thus supporting its use as a complement to clinical assessment.

Without a widely agreed upon standard protocol for postoperative flap monitoring and without national data on monitoring trends in the last ten years, the purpose of this survey was to learn how microvascular surgeons were managing patients postoperatively, assess the number of individuals still utilizing clinical assessment as their primary gauge of flap health and discover the openness of these individuals to new monitoring techniques.

MATERIALS AND METHODS:

1. Capillary Blood Gas Assessment of Free Flap Perfusion

This portion of the thesis was completed by Aaron Remenschneider and Greg Lesnik (Otolaryngology resident) with technical assistance from Dr. Peter Herman, neurophysiology.

After receiving Institutional Animal Care and Use Committee (IACUC) approval, 10 male Sprague Dawley rats weighing roughly 300 g were purchased. All animals were housed in accordance with the Yale Animal Committee standards in the preoperative time period. During the experiment, animals were anesthetized with an intraperitoneal injection of ketamine 90mg/kg and xylazine 5mg/kg body weight. Level of anesthesia and respiratory status were continually monitored. Repeat injections of ketamine 45mg/kg and xylazine 2.5mg/kg body weight were given for animal arousal prior to completion of the study. Animals were then placed on a heating mat warmed to 37.5 degrees Celsius. Core body temperature was continually measured via a rectal thermometer. Clean techniques were employed as sterility was not essential. Rats were euthanized at the completion of each experiment via lethal injection of pentobarbital at 150mg/kg per IACUC protocol.

Surgical Procedure

Bilateral abdomen and groin sites were shaved. A groin fasciocutaneous flap was then elevated and completely detached from surrounding tissues ranging vertically from the costal cartilage to mid-thigh and horizontally from just lateral to midline to the axillary line. The epigastric artery and vein were then carefully identified and followed to their insertion on the femoral vessels. Using an operating microscope, the sheath of the epigastric vessels was entered, epigastric nerve divided and artery and vein separated. The femoral sheath was similarly isolated. All flaps revealed a visible arterial pulse along the length of the epigastric artery post-operatively. The flap was then fastened to

the abdomen of the rat to prevent movement and ensure warming. Following completion of experimentation on one side a contralateral groin fasciocutaneous flap was then elevated in the same manner.

Venous clamping was performed by placing a microclamp around the epigastric vein just proximal to its insertion on the femoral vein under direct microscopic visualization. Care was made not to contact or stretch the artery. Proper placement was confirmed by visual lack of blood distal to the clamp and visualization of a persistent pulse in the epigastric artery. Arterial clamping was performed by similarly placing a microclamp around the epigastric artery. Successful clamp placement was confirmed by lack of pulsation distal to the clamp.

Oxygen Microelectrode Measurements

Bare Fibre pO_2/Temperature Sensor type microelectrodes with a tip diameter of 4um were used (Oxford Optronix OxyLab, Oxford, UK). Microelectrodes were attached to the OxyLite/OxyFlo combined channel monitor for interpretation (Oxford Optronix OxyLab, Oxford, UK). Continuous measurements of pO_2, flow and temperature were measured and recorded on a desktop computer using *Spike2* software (Cambridge Electronic Design, Cambridge, UK). Tissue oxygen levels are determined by the flourescence quenching principal where bursts of LED light transmitted via fiberoptics excite a platinum based dye in the electrode tip, resulting in emission of fluorescent light which is absorbed by local oxygen molecules. The difference between absorbed and measured reflected light represents local oxygen tension. Tissue flow is determined via Laser Doppler Flowmetry [LDF] where light from the probe tip is projected into the

tissue, scattered and then reabsorbed by a sensor. Properties of reflected light from erythrocytes and stationary tissues differ, representing the Doppler shift, and can be interpreted as local flow over time by the OxyFlo monitor. The numeric calculation of LDF is based on the concentration of local red blood cells and the velocity at which they travel. Local temperature is determined by an attached thermocouple transducer.

Capillary Blood Gas Measurements

CBG measurements were obtained using heparanized capillary tubes and an ABL5 Capillary Blood Gas Monitor (Radiometer Copenhagen, Copenhagen Denmark).

Capillary Blood Gas Assessment of Free Flap Perfusion: Experimental Protocol

A. Tissue Oxygen Tension:

Using stereotactic manipulators, the oxygen microelectrode was inserted into the fascia to a depth of approximately 1mm. Electrodes were consistently inserted 5mm lateral to the split in the epigastric pedicle. Continuous readings of pO_2, flow and temperature were confirmed and recorded. Flaps were allowed to equilibrate for approximately 20 minutes or until steady state values were obtained for all 3 parameters. Venous (n=4) or arterial (n=3) clamping was then performed as previously mentioned. Measurements were continually recorded for 20 minutes. Due to technical difficulties successful readings were obtained from 5 flaps following occlusion: venous (n=3), arterial (n=2).

B. Capillary Blood Gas Measurements:

Flaps were allowed to equilibrate for 20 minutes following surgery. CBG measurements were then obtained via the following manner. Under direct microscopic visualization, the epigastric vein adventitia was grasped using Jewlers forceps. A 30 gauge needle with attached heparinized 1cc syringe was then carefully used to cannulate the epigastric vein. Approximately 100 microliters of blood were then aspirated directly from the vein. Blood samples were then transferred into a heparinized capillary tube and inserted into the ABL5 blood gas machine for measurement of pH, pO_2 and pCO_2. Further blood loss from the puncture site was prevented by applying gentle pressure using a cotton tipped applicator.

In the experimental arm, following venous occlusion, repeat CBG measurements were obtained at 10 and 20 minutes. CBG measurements were obtained in a similar manner by again cannulating the epigastric vein with a 30 gauge needle distal to the microclamp. Approximately 100 microliters of blood were gently aspirated directly from the vein within a 1 minute time period. Adequate perfusion was confirmed prior to obtaining blood samples by the visible presence of a pulse in the epigastric artery leading to the flap. CBG readings obtained with less than 100 microliters of blood produced erroneous results and were therefore immediately repeated by reaspirating a sufficient sample from the epigastric vein. Due to technical constraints largely stemming from the small caliber of the epigastric vein and inherent trauma from repeated cannualization several data points were missed.

Capillary Blood Gas Assessment of Free Flap Perfusion: Analysis of Data

CBG measurements were recorded and the values of pO_2, pH and pCO_2 as well as HCO_3 (calculated: Henderson Hasselbalch equation) at 0, 10 and 20 minutes following venous clamping in all eight flaps. Data on average CBG measurements or standard deviations for pH and pO_2 are not available for an a priori power analysis; thus, using sample sizes reported in the literature for similar research(31, 33, 34, 37) and a post hoc power analysis, we reached power over 95 percent in both pH and pO_2 samples. Changes from pre-clamp controls were statistically evaluated using a two-tailed paired Students *t* test and the Wilcoxon signed rank test. Statistical significance was defined as a *P* value <0.05. Data were analyzed using SPSS software and with the support of Yale University Statistics Laboratory.

2. Yale National Survey of Free Flap Monitoring Technique

This portion of the thesis was completed by Aaron Remenschneider, under mentorship from Dr. Douglas A. Ross, Section of Otolaryngology.

Development of the Survey

After consulting the small body of literature on institutional and surgeon use of various flap monitoring techniques, a library of common questions used in these surveys was constructed. 'Clinical Assessment' techniques, also known as subjective monitoring techniques were differentiated from 'Objective' monitoring techniques that rely on a specified and measured parameter of the tissue. Monitoring devices and techniques included were those found in the literature as well as recently reported innovations from

2002-2007. Surgeons were asked whether they preferred “clinical assessment’ to ‘objective’ monitoring. They were also asked whether they would be open to new monitoring devices, if they worked at resident staffed hospitals and who was responsible for post-operative care of patients with free flaps. Additionally, the survey asked about the volume of reconstructive cases, whether costs were a consideration in monitoring technique and whether staff training was a barrier to new surveillance practices. All questions were multiple choice and allowed respondents to select more than one response where appropriate. Each question also allowed for both write in responses and commentary on the question.

Distribution of the Survey

The survey was built with the help of the Professional edition of the online survey creation tool, SurveyMonkey (SurveyMonkey.com Corporation, Portland, OR). Contact information for reconstructive surgeons from the 200 largest head and neck reconstructive centers was obtained from Chris Ubinger of Metronic Corporation. 238 email addresses were obtained and entered into the online survey database. An initial email with a short introduction of the study’s purpose introduced the online survey followed by a web-link to direct participants to the SurveyMonkey website. The online survey was open for response for 30 days. One follow up email was sent to non-respondents at the two-week mark. Only one response per surgeon was accepted. Overall response rate was 42% (99/238).

Collection of Survey Data

All survey data was collected with the support of SurveyMonkey Professional edition (SurveyMonkey.com, Portland, OR), which allows for the creation of charts, graphs and analysis by response type.

RESULTS:

1. Capillary Blood Gas Assessment of Free Flap Perfusion

Oxygen Microelectrode, Venous Clamping

Mean oxygen tension prior to venous clamping was 28.53 mmHg with a mean flow of 317 (Table 1). A clear steady state without fluctuations in pO_2 or flow were observed in all experiments at 20 minutes post-procedure. Venous clamping resulted in a gradual decline in pO_2 across all time points. At 5, 10 and 15 minutes mean pO_2 was 23.73 mm Hg, 17.50 mm Hg and 16.26 mm Hg, respectively. Similarly venous clamping resulted in decreased flow across all time points. At 5, 10 and 15 minutes mean flow was 288, 280 and 249 respectively. Average decline in pO_2 from control at 15 minutes was 12.27 mm Hg. Figure 1 demonstrates the steady state pO_2 at 20 minutes and the gradual decline in both pO_2 and flow following venous clamping.

Arterial Clamping

Mean oxygen tension prior to arterial clamping was 18.85 mm Hg with a mean flow of 497.5 (Table 1). Arterial clamping resulted in a rapid decline in pO_2 from steady state values. Similarly, the 5 minutes mean flow decreased from 497 to 153. Figure 2

demonstrates the steady-state pO_2 at 20 minutes and the rapid decline in pO_2 and flow following arterial clamping in one experiment.

Capillary Blood Gas Measurements:

Serial CBG measurements at control and over time following venous clamping may be found in Table 2. Mean pO_2 prior to venous clamping was 42.71 (+/- 5.12) mm Hg. Following venous clamping, mean pO_2 measurements at 10 and 20 minutes declined to 31.57 (+/- 7.83) mm Hg and 28.67 (+/- 6.28) mm Hg, respectively (Figure 3). Subjecting the data to a two tailed, paired Student's *t* test, this negative change in pO_2 over the course of the first 10 minutes was statistically significant at the $P < 0.05$ level ($t(5) = 3.733$, $*P = 0.014$, 95% CI = (3.74, 20.26)) (Table 3), and the decline continued over the following 20 minutes ($t(4) = 13.870$, $*P < 0.001$, 95% CI = (14.72, 22.08)). The Wilcoxon signed rank test demonstrated CBG successfully detected falling pO_2 in seven of seven flaps at 10 minutes postclamp ($P < 0.001$). This was also true at 20 minutes when six of six pO_2 values had dropped ($P < 0.001$).

Mean pH prior to venous clamping was 7.38 (+/- 0.04). Following venous clamping pH measurements at 10 and 20 minutes decreased to 7.33 (+/- 0.05) and 7.30 (+/- 0.04), respectively (Figure 2). The negative change in pH during the first 10-minute period was statistically significant at the $P < 0.05$ level using the Student's *t* test ($t(6) = 2.997$, $*P = 0.024$, 95% CI = (0.01, 0.16)) (Figure 4). The Wilcoxon test showed CBG detected falling pH in six of seven flaps at 10 minutes ($P = 0.031$), and in five of six flaps at 20 minutes ($P = 0.062$).

Mean CO_2 and HCO_3 prior to venous clamping were 41.13 (+/- 7.68) mm Hg and 23.38 (+/- 3.11) respectively. Following venous clamping pCO_2 decreased at 10 minutes to 39.00 (+/- 9.80) mm Hg and had increased at 20 minutes to 43.50 (+/- 6.28) mm Hg. HCO_3 decreased from control at 10 and 20 minutes to 21.16 (+/- 3.66) and 21.17 (+/- 6.11). Neither parameter showed significant changes over time (Table 3). The Wilcoxon test did not find significance for the changes in either CO_2 or HCO_3.

2. Yale National Survey of Free Flap Monitoring Technique

Respondents

An electronic invitation to participate in the Yale Free Flap Monitoring Survey was sent to 238 individuals at academic and private practice medical centers nationwide. Of the 238 distributed, 99 surveys were completed online for a response rate of 42 percent. All 99 of those who started the survey completed it. 82 of the 99 or 84.5 percent indicated that they worked in academic institutions staffed with residents (Figure 5). 65.7 percent of respondents stated that nurses provide the majority of free flap monitoring post-operatively, while 23.2 percent stated it was resident house-staff that did the majority of monitoring (Figure 6). Attending surgeons and microvascular fellows were found to be less frequently involved in flap monitoring. Nurses were found to provide the majority of postoperative flap care and surveillance regardless of whether the surgeon worked at an academic center or in a private group. 33 percent of respondents perform more than 50 free flap reconstructions per year while 45.5 percent perform less than 30 per year (Figure 7). Respondents not working in academic medical centers tended to perform fewer free flaps per year than those in academic centers (Figure 8).

Monitoring Technique

All respondents indicated that they utilize clinical assessment in postoperative flap surveillance. At 98 and 97 percent, nearly all surgeons use capillary refill and flap color as markers of flap health, respectively (Figure 9). Three respondents commented that subjective temperature (taken with the back of a knuckle) was also an important clinical assessment technique used in their practice. 98 percent of respondents also use adjunctive measures to monitor flap health. 55.7 percent employ pin-prick tests, 44.3 percent use laser Doppler and 21.2 percent use the hand held Doppler ultrasound (Figure 10). Other adjunctive monitoring techniques were used with lower frequency. When asked to prioritize clinical assessment or adjunctive testing, 74.7 percent preferred clinical assessment as described in question 1 of the survey (Figure 11). 15 percent indicated that they rely heavily on both.

When separated by institutional affiliation, 60 percent of academic microvascular surgeons indicated they use pin-prick assessment while only 26.7 percent of private reconstructive surgeons do (Figure 12). There is also a wider distribution of techniques among private surgeons and higher percent (30%) use temperature monitoring whereas only 10 percent of academic surgeons use this. Private microsurgeons are also twice as likely to rely on adjunctive monitoring tests in the decision to take a flap back for revision when compared to academic microvascular surgeons.

Monitoring Staff and Openness to New Technique

89.9 percent of respondents suggested that they would be open to different monitoring techniques (Figure 13), and 67.7 percent indicated that staff training would not be a

barrier to the implementation of new monitoring technologies (Figure 14). If a new monitoring device was to be considered, 67.7 percent of respondents stated that the expense of the device would be a factor into their willingness to adopt the piece of equipment (Figure 15). These did not differ significantly between academic and private microvascular surgeons.

DISCUSSION:

For many patients undergoing head and neck oncologic resection free tissue transfer remains the best reconstructive option. Despite technological advances, flap failure rates due to arterial and venous thrombosis still approximate 5%.(20, 21) Studies have clearly shown tissue failure from ischemia occurs in two parts: acutely due to the initial hypoxia with ensuing acidosis and later due to reperfusion injury more commonly referred to as no-reflow phenomenon.(22-24) Research has demonstrated that the no-reflow phenomenon may occur in as little as 6 hours.(22) If flap perfusion is found to be impaired prior to this critical time, flap salvage is an option with reported success rates ranging from 69- 95%.(20, 25, 26) Because of the narrow window of time available to correct impaired perfusion, flap surveillance in the post-operative time period is paramount.

Adjunctive Monitoring Techniques

Numerous postoperative flap-monitoring techniques have been developed and trialed over the years; however, most harbor limitations, thus curbing their utility in practice. The last surveys conducted of reconstructive centers over 10 years ago clearly

demonstrated that no one technique is commonly employed and that clinical assessment remains the gold standard for monitoring flaps post-operatively.(23, 27, 45) Adjunctive surveillance strategies currently used target 1 of 3 physiologic aspects of the flap: flow, temperature or oxygen tension. Tissue flow may be monitored primarily in the pedicle using hand held Doppler ultrasound probes or implantable Doppler flow systems (28) or flow may be monitored in smaller vessels within the tissue using laser Doppler flowmetry.(25, 29) Results and opinions on the effectiveness of these techniques however have varied.

Directly measuring oxygen tension within tissues is another accepted technique for monitoring flap perfusion. In this experiment flap failure due to arterial or venous occlusion was observed in the relatively short time frame of 10 and 15 minutes. Furthermore, the differences in the measurement of flow by oxygen microelectrode recorded two clearly distinct patterns between arterial and venous compromise (Figures 1 and 2). These results are consistent with experiments done in humans that successfully identified impaired perfusion, (31, 32) and our experience with the probes validated the difficulty of operating and interpreting data from the microelectrode. While distinguishing between arterial and venous compromise is helpful, most studies suggest clinical assessment can quickly identify arterial compromise as distinct from venous congestion.(20, 23, 27, 45) Unfortunately, the major limitations of the microelectrode technique remain the costs and the fragility of the oxygen probes.

One early monitoring technique attempted to directly analyze the acid base status of the flap by following pH with an implantable probe.(33, 34) With more advanced technology today, we are now able to directly monitor the physiologic milieu of the

transferred tissue, observing for changes in biochemical markers as evidence of ischemia.(35) While the effectiveness of such experimental techniques has been validated in highly controlled and small studies, the costs, both economic and practical remain high.

Reported estimates of proposed monitoring devices include the laser Doppler flowmeter ($10,500 + 1200/year),(25) the Microdialysis catheter and analyzer ($26,000 + 350/patient),(35) or the oxygen microelectrodes ($300-$400/use/patient).(31) We can contrast that with the cost of the capillary blood gas, which is dependent only on the equipment necessary to obtain the sample and analyze the result: a 20 gauge needle (~3 cents), a heparinized capillary tube (~5 cents), and the capillary gas machine (nearly ubiquitous in hospitals today).

Capillary Blood Gas in the Assessment of Flap Perfusion

In this experiment, postocclusive changes in oxygen tension and pH were detected with capillary blood gas analysis. Raskin and colleagues suggest that continuous monitoring of pH after selective occlusion of the epigastric vessels will result in predictable falls in pH measurements over time with the ensuing acidosis.(33, 34) The results from our experiments paralleled these falls in pH and suggest that CBG is a sensitive indicator of acidosis and cellular hypoxia. The observed changes in pH are likely due to increasing lactate levels as cells shunt the products of glycolysis towards anaerobic respiration with decreasing available O_2.(46) Changes in measured pO_2 values via CBG following venous occlusion in our experiment were statistically significant and directly mimicked the changes observed using the oxygen microelectrode system (Tables 1 and 2). The pCO_2

and calculated HCO_3 levels did not show statistically significant changes over time in this model (Table 3). While cellular physiology would predict rising pCO_2 in congested flaps, local HCO_3 from arterial blood may have buffered this rise, blunting our observed pCO_2 trends over 20 minutes. Larger and consistent changes in pCO_2 may be observed in flaps followed for longer periods.

Limitations

Rat groin flaps with epigastric pedicles have long been used to simulate fasciocutaneous pedicle and free flaps.(47, 48) The elevation of the entire flap, leaving only the vascular pedicle allows simulation of arterial clotting or venous thrombosis, with concurrent preservation of inflow or outflow from the flap. This manipulation creates a flap microenvironment similar to failing fasciocutaneous free flaps in humans. Because of the urgency required to salvage a failing flap, oxygen tension has often been suggested as an ideally sensitive measure of flap health. Several studies have shown oxygen tension to be a reliable indicator of flap perfusion.(37, 49-51) However, measured values of the partial pressure of oxygen in the tissue varies based on sampling site, distance from vessel insertion, warmth, and degree of rubbing.(46, 52, 53) Keeping these principles in mind, our study design attempted to ensure uniform warmth, uniform oxygen electrode placement and minimal irritation to both the flap and vascular pedicle.

While our original goal had been to measure flow and oxygen tension with the microelectrode and simultaneously sample serial capillary blood gases from the groin flap skin, we were limited by both the fragility of the microelectrode and the inadequate volume of blood available from local tissues upon laceration. By separating our

procedure into two steps, our pO_2 and Doppler flow readings from the microelectrode demonstrated a healthy pedicle flap with successful arterial and venous clamping technique (Figures 1 and 2). Furthermore, it indicated the appropriate postoperative flap recovery time was 20 minutes. This ensured a stable, baseline flap perfusion in the CBG model, and confirmed that reliable control values could be taken with confidence prior to vessel perturbation.

Because of the limitations of flap size, skin thickness and inadequate local flow parameters, adequate capillary blood gas samples could only be obtained via epigastric vein cannulation. This was primarily a result of the small size (3cm x 3cm) and constrained blood flow volume to the rat flap. While this technique does not directly simulate tissue sampling, it does provide valuable information on the microenvironment of the flap. Experimentation in an animal model with a larger flap size (ie: pig) or direct sampling from pin-prick assessment in humans would clearly allow adequate blood for the capillary blood gas. While extrapolation of our data would suggest that measured changes in pH and pO_2 from venous samples should also be observed from samples taken directly from the tissue, this can not be proven in this study. Importantly, it was our observation that it was not the absolute values of pH and pO_2 that were predictive, but instead the changes between values taken over time.

The response rate of our survey was somewhat limited at 44%, with 85% of respondents working at resident staffed hospitals. Given that our database of contacts was cited to be a roughly 70% academic and 30% private, there was a greater likelihood of response among academic surgeons. Unfortunately our survey was conducted unknowingly on the heels of another national survey of the same kind and it is possible

that some recipients suffered from survey fatigue. Furthermore, the contacts were obtained from Chris Ubinger, a representative from the industry side of medicine, who compiled the list from the 200 most active reconstructive centers. Since we did not capture from the entire universe of reconstructive surgeons, we may have missed important constituents who do not practice in ways paralleling our respondents.

While most head and neck oncologic resections and reconstructions are carried out in an academic center, the underreporting from non-academic surgeons may have skewed the survey results. This bias may be evident in the perceived surgeon openness to new techniques and availability of support staff for flap monitoring.

Application of Capillary Blood Gas in Practice

It is commonly stated that the ideal free-flap surveillance technique will be reliable, user friendly, inexpensive and consistent.(19) As of yet, no technique satisfies all these criteria. It was our objective to evaluate the capillary blood gas in this capacity, because CBG currently fulfills these criteria in the pediatric/neonatal care setting by virtue of being minimally invasive, inexpensive, and reliable. The measurements of pH, pCO_2, and pO_2 are easily obtained and have proven highly correlated among ABG, VBG and CBG.(43, 44) A simple prick of the flesh provides several drops of blood that can be drawn into a capillary tube and analyzed with either a hand-held or lab-based blood gas machine, usually located near neonatal or cardiac units in-house. Pricks can be performed as needed or on a standardized schedule to chart oxygen and acid/base status over time.

With 55 percent of survey respondents noting that they use pinprick and bleeding rate already as an adjunctive flap monitoring technique, the act of collecting the blood in

a capillary tube for blood gas analysis comes at little cost to the patient or health provider. In 1995, Urken described clinical assessment by an experienced microvascular surgeon as the most effective means of surveillance.(27) Unfortunately, given the nation's volume of head and neck cancer, not all patients are able to receive care at large cancer hospitals, and this was demonstrated in the survey - 45% of free flaps are performed at low volume centers (performing < 30 flaps/year). While success rates for free tissue transfer are widely reported above 95%(19, 54) this success has been repeatedly shown to be correlated with the experience of the surgeon.(20, 26) If clinical assessment is to continue as the gold standard for flap monitoring, then individuals at low volume centers will be at a distinct disadvantage. Thus the question is whether the capillary blood gas can help detect flap failure when clinical observation cannot, and certainly this is most relevant for microvascular surgeons performing few flap procedures each year.

This survey demonstrated that private surgeons perform fewer free flap operations than do academic surgeons (Figure 8), and it also showed that private surgeons have different preferences for flap surveillance (Figure 12). It stands to reason that private surgeons at low volume centers are likely the best candidates for the adoption of the capillary blood gas. Furthermore, the simplicity, low cost and reliability of the capillary blood gas coincide with the preferences indicated by both private and academic microvascular surgeons in this survey (Figures 13, 14, 15).

Despite technological advances, free tissue transfer still maintains a failure rate unacceptable to reconstructive surgeons. Post-operative flap surveillance strategies provide the best opportunity for identifying and salvaging flaps with impaired perfusion.

To date, there remains no universally accepted post-operative monitoring technique to complement clinical assessment of the transferred tissue. The field of reconstructive surgery needs a uniform method of collecting objective and reliable data, one user-friendly enough to be employed with minimal training by ancillary health care staff. In this study, capillary blood gas proved to be a powerful tool for evaluating impaired perfusion to a flap because it provides users the ability to simultaneously monitor two accepted methods of flap surveillance: pO_2 and pH, while doing so in an inexpensive and reliable manner. The finding that the simple CBG is a useful monitoring tool carries significant weight and should merit further evaluation in humans.

APPENDICES

Appendix 1.

Oral Cavity and Oropharynx

Tis	Carcinoma is *in situ*
T1	Tumor is 2 cm or less in greatest dimension
T2	Tumor is more than 2 cm but not greater than 4 cm in greatest dimension
T3	Tumor is more than 4 cm in greatest dimension
T4a	Tumor invades adjacent structures: cortical bone, muscle of tongue, larynx, medial pterygoid, hard palate or mandible
T4b	Tumor invades masticator space, pterygoid plates, or skull base and/or encases the internal carotid artery

Supraglottis

T1	Tumor is limited to one subsite of the supraglottis, with normal vocal cord mobility
T2	Tumor invades mucosa of more than one adjacent subsite of the supraglottis or glottis, without fixation of the larynx
T3	Tumor is limited to the larynx with vocal cord fixation and/or invades the postcricoid area, pre-epiglottic tissues, paraglottic space and/or thyroid cartilage erosion
T4a	Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (trachea, soft tissues of neck, strap muscles, thyroid, esophagus)
T4b	Tumor invades prevertebral space, encases the carotid or invades the mediastinum

Glottis

T1	Tumor is limited to the vocal cords with normal mobility
T2	Tumor extends to the supraglottis and/or subglottis and/or with impaired vocal cord mobility
T3	Tumor is limited to the larynx with vocal cord fixation and/or invades paraglottic space, and or minor thyroid cartilage erosion
T4a	Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (trachea, soft tissues of the neck, strap muscles, thyroid, or esophagus)
T4b	Tumor invades prevertebral space, encases the carotid or invades the mediastinum

Subglottis

T1	Tumor is limited to the subglotttis
T2	Tumor extends to the vocal cord(s), with normal or impaired mobility
T3	Tumor is limited to the larynx, with vocal cord fixation
T4a	Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (trachea, soft tissues of the neck, strap muscles, thyroid, or esophagus)
T4b	Tumor invades prevertebral space, encases the carotid or invades the mediastinum

Hypopharynx

T1	Tumor is limited to one subsite of the hypopharynx and 2cm or less in dimension
T2	Tumor invades more than one subsite of the hypopharynx or an adjacent site, or measures more than 2 cm but not more than 4 cm in greatest dimension without fixation of the hemilarynx
T3	Tumor is more than 4 cm in greatest dimension or with fixation of the hemilarynx
T4a	Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, esophagus, or central compartment soft tissue
T4b	Tumor invades prevertebral fascia, encases the carotid or involves the mediastinum

Lymph Node Staging for Oral Cavity, Oropharynx, Hypopharynx and all Glottic Cancer

N0	There is no regional nodes metastasis
N1	Metastasis is in a single ipsilateral lymph node, 3cm or less in greatest dimension
N2	Metastasis is in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or metastasis is in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension or bilateral or contralateral lymph nodes (although less than 6 cm)
N2a	Metastasis is in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm
N2b	Metastasis is in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis is in bilateral or contralateral lymph nodes, none more than 6 cm
N3	Metastasis is in a lymph node more than 6 cm in greatest dimension

Stage Grouping

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
Stage IVB	T4b	Any N	M0
	Any T	N3	M0
Stage IVC	Any T	Any N	M1

Appendix 2.

Yale Free Flap Monitoring Survey

1. Which of the following clinical assessment techniques do you use to assess cutaneous free flap viability post-operatively? (Select all that apply)
   - Capillary refill
   - Flap Color
   - Skin Turgor
   - Tissue Edema
   - I do not rely on clinical assessment of flap viability
   - Other

   Comments:

2. Which of the following objective measures do you use in assessing flap viability post-operatively?
   (Select all that apply)
   - Implantable Doppler Cuff at vascular pedicle
   - Intravenous Sodium Fluorescein monitoring
   - Lancet (prick) and Bleeding
   - Microdialysis
   - Muscle contractility testing
   - Non-Invasive Laser Doppler Ultrasonography
   - Photoplethysmograph
   - Plethysmograph
   - Pulse Oximetry
   - Temperature monitoring
   - Transcutaneous O2 monitoring
   - Tissue Oxygen Tension (microelectrodes)
   - Tissue pH monitoring
   - Tissue Spectrophotometry
   - Other:

   Comments:

3. Are clinical assessment techniques or objective measures more important to you in making the decision to re-explore the vascular pedicle in a threatened flap?
   - Clinical assessment
   - Objective Tests

   Comments:

4. Would you be open to using a different objective monitoring technique?
   - Yes
   - No

5. Is the expense of objective monitoring techniques a consideration in your choice of instruments?
   - Yes
   - No
6. Is staff training a barrier to the use of newer, free flap objective monitoring technologies?
   - Yes
   - No

7. Any other comments about post operative monitoring of free tissue flaps:

DATA TABLES

Table 1. Oxygen Microelectrode Measurements Obtained After Vein or Artery Clamping

Measure		Vein (n=3)	Artery (n=2)
Oxygen tension (mmHg)			
	Before Clamp	28.53	18.85
	5 Minutes	23.73	6.56
	10 Minutes	17.5	7.57
	15 Minutes	16.26	8.47
Blood Flow (LDF)			
	Before Clamp	317	497
	5 Minutes	288	153
	10 Minutes	280	119
	15 Minutes	249	148

Table 2. Capillary Blood Gas Measurements Obtained After Vein Clamping: Mean +/- 1 Standard Deviation

Vein Clamp (n=8)	Time	pO_2 (mmHg)	pH	pCO_2 (mmHg)	HCO_3
	Before clamp	42.71 (+/- 5.12)	7.38 (+/- 0.04)	41.13 (+/-7.68)	23.38 (+/- 3.11)
	10 Minutes	31.57 (+/- 7.83)	7.33 (+/- 0.05)	39.00 (+/- 9.80)	21.16 (+/- 3.66)
	20 minutes	28.67 (+/- 6.28)	7.30 (+/- 0.04)	43.50 (+/- 11.20)	21.17 (+/- 6.11)

Table 3. Statistical analysis of changes in Capillary Blood Gas measurements from control at 10 and 20 minutes following venous clamping using the paired t-test.

Time Interval	Statistical Value	pO_2 (mmHg)	pH	pCO_2	HCO_3
Time 0-10 min					
	p value	*0.014	*0.024	0.539	0.227
	DF	5	6	6	6
	95% CI	(3.74, 20.26)	(0.0008, 0.080)	(-5.51, 9.51)	(-1.51, 5.20)
Time 0-20 min					
	p value	*<0.001	*0.032	0.65	0.523
	DF	4	5	5	5
	95% CI	(14.72, 22.08)	(0.01, 0.16)	(-20.26, 13.93)	(-5.59, 10.28)

*$p<0.05$, DF=degrees of freedom, CI=confidence interval

FIGURES

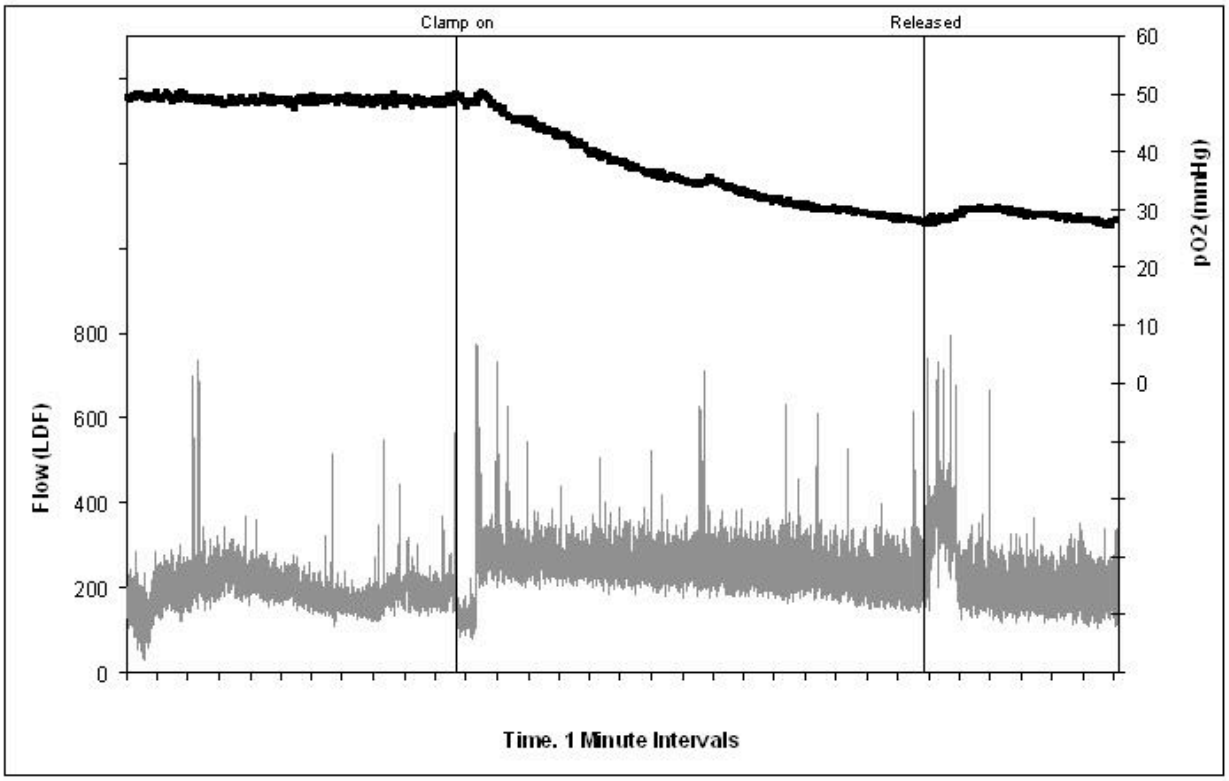


Figure 1 A typical recording performed with the Bare-Fibre Oxygen Microelectrode showing oxygen tension (pO_2, mm Hg) and flow (perfusion units) before, during and after venous clamping

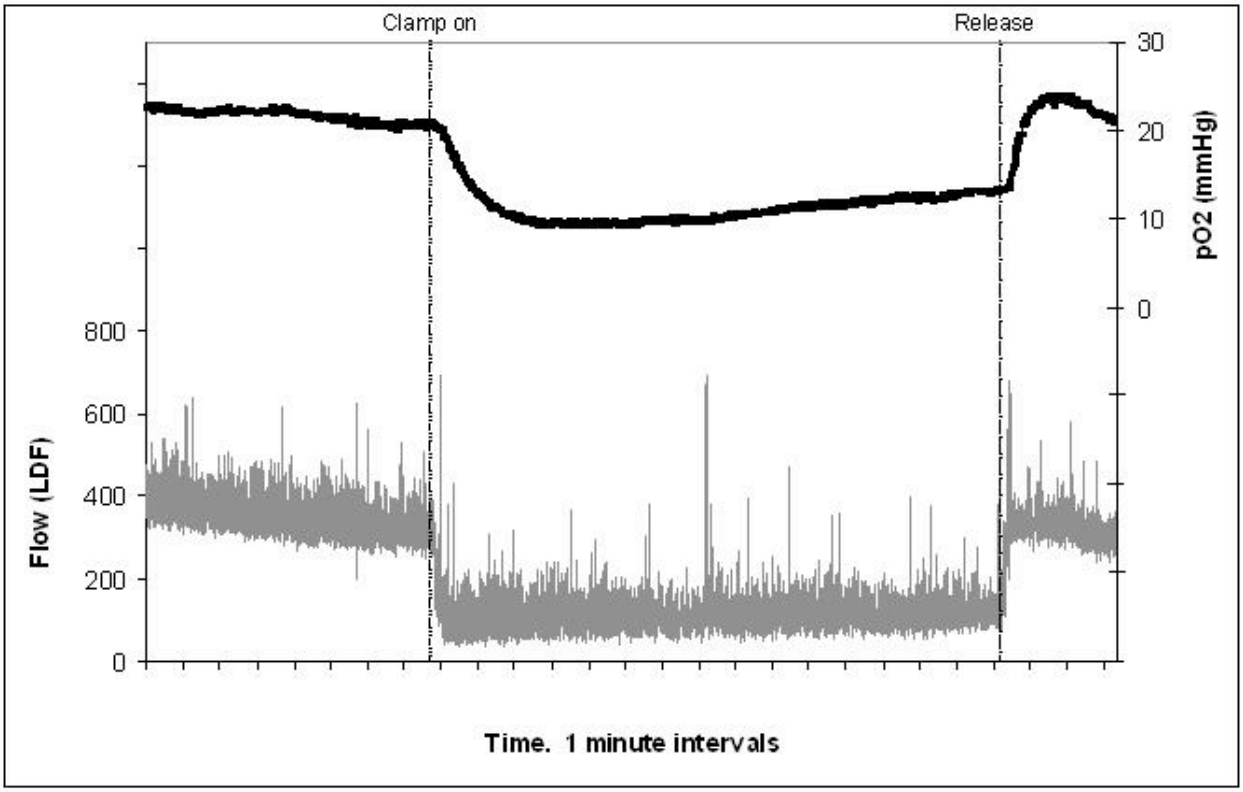


Figure 2 A typical recording performed with the Bare-Fibre Oxygen Microelectrode showing oxygen tension (pO_2, mm Hg) and flow (perfusion units) before, during, and after arterial clamping.

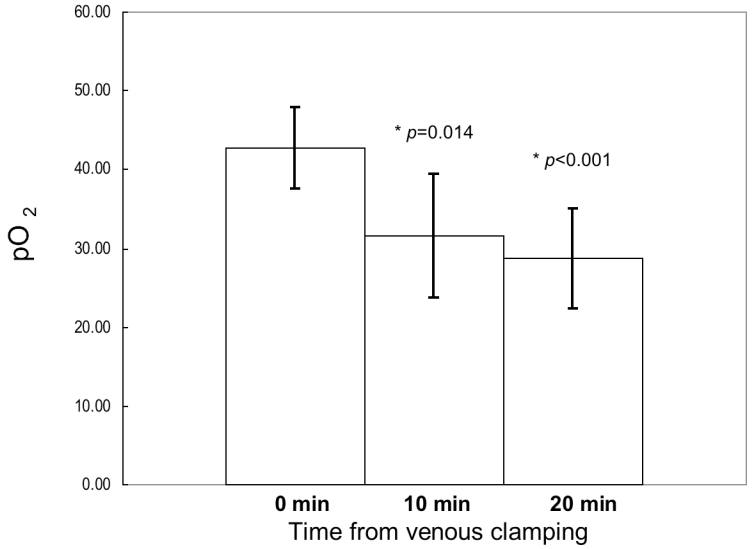


Figure 3. Changes in CBG pO_2 measurements from control at 10 and 20 minutes following venous clamping. Error bars represent 1 SD. * $p<0.05$.

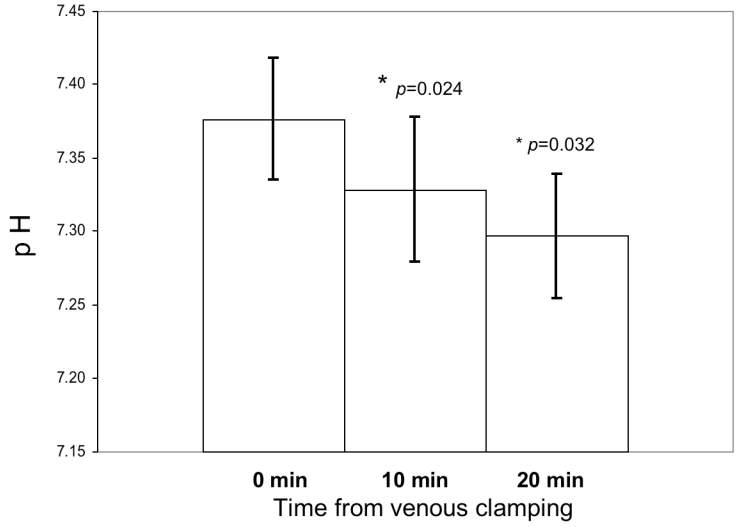
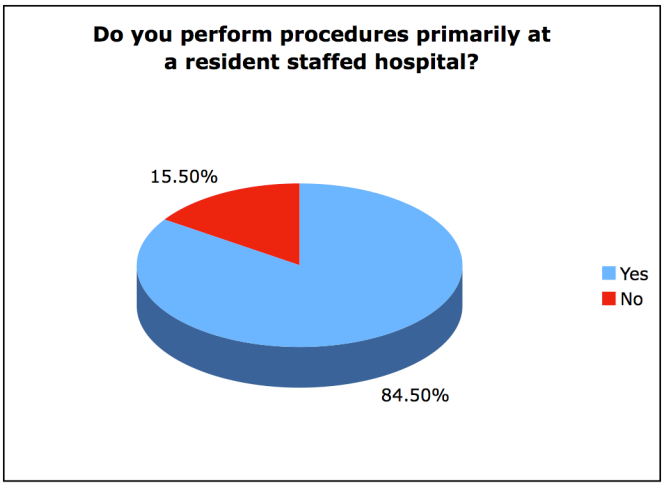


Figure 4. Changes in CBG pH measurements from control at 10 and 20 minutes following venous clamping. Error bars represent 1 SD. * $p<0.05$.

Figure 5.



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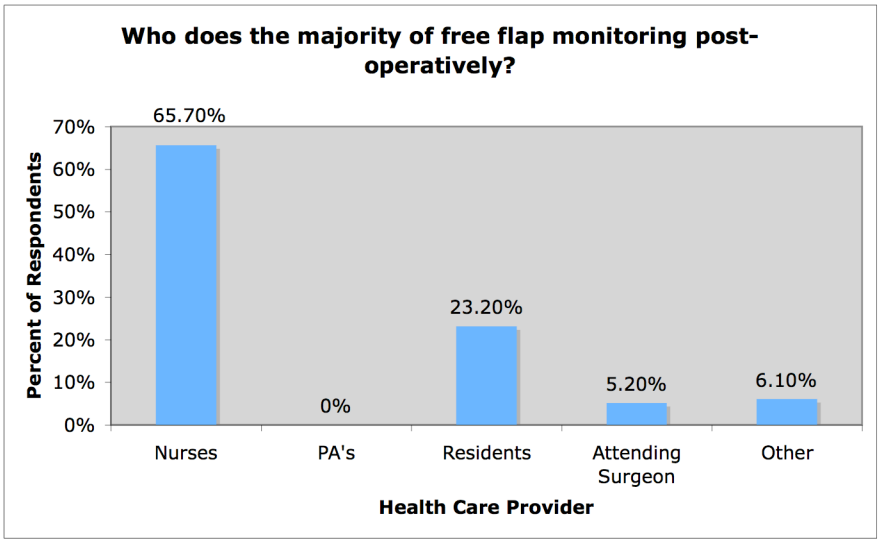

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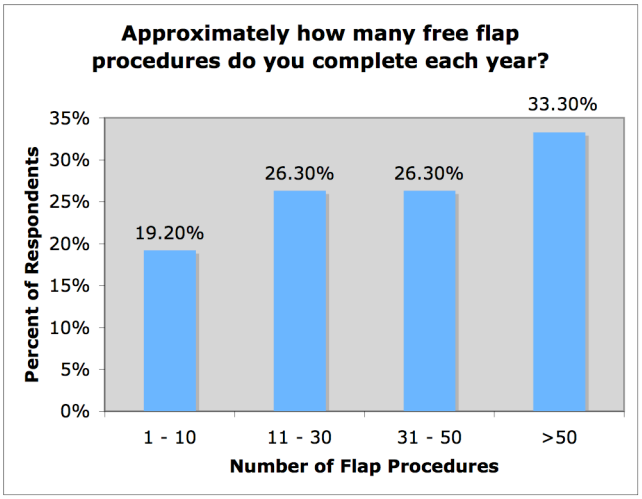

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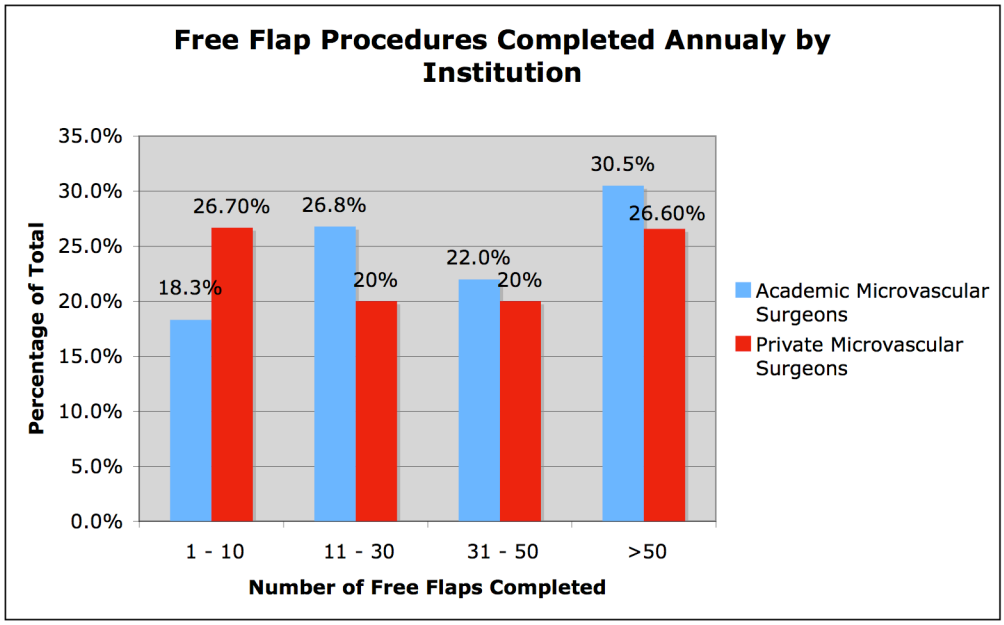

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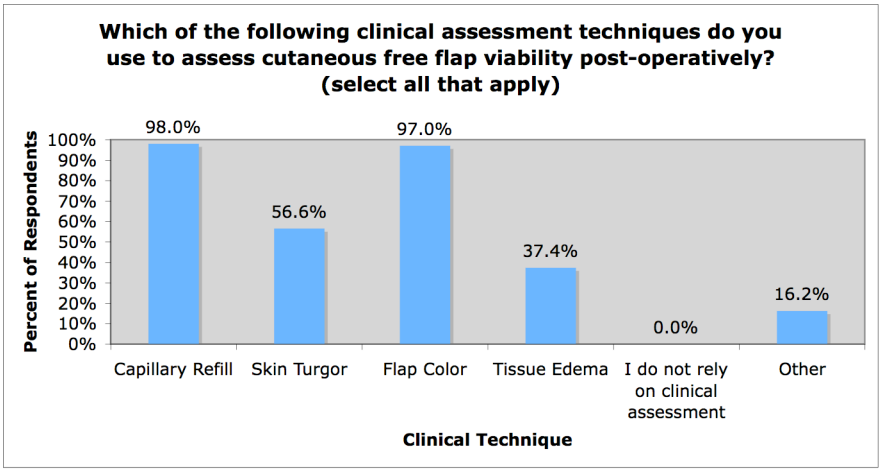

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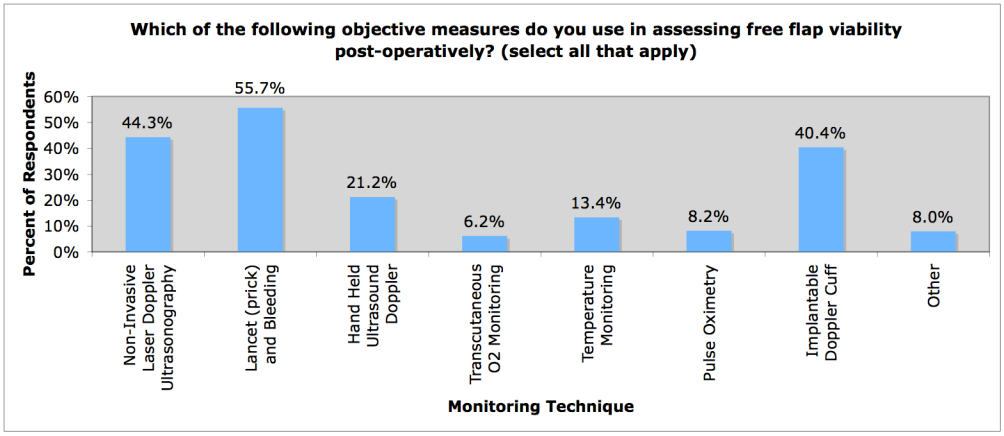

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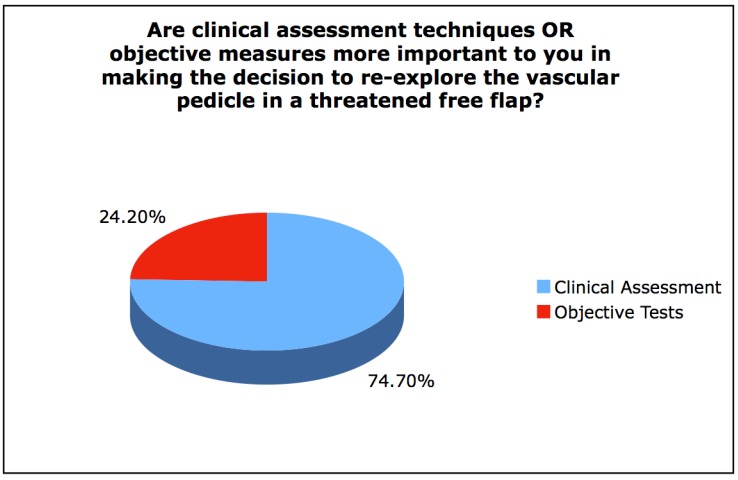

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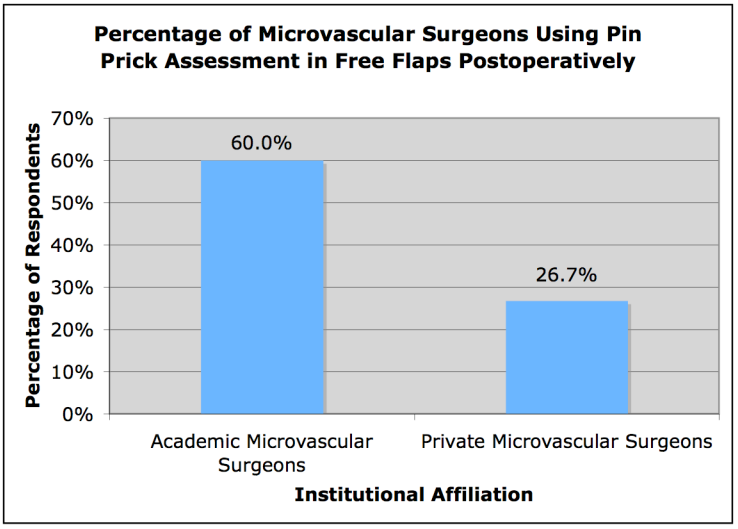

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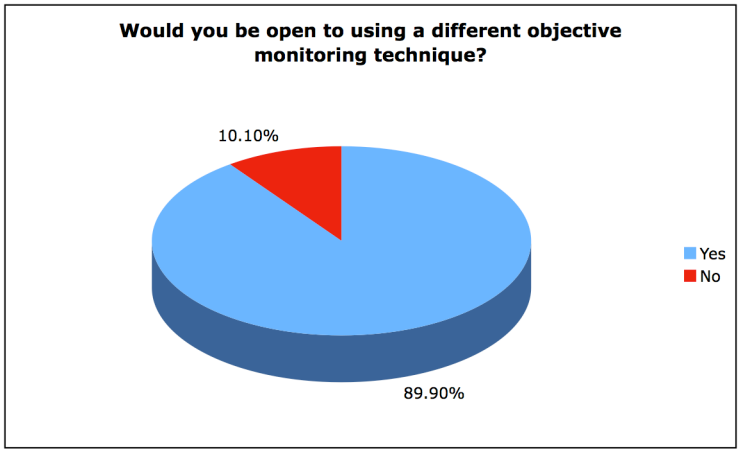

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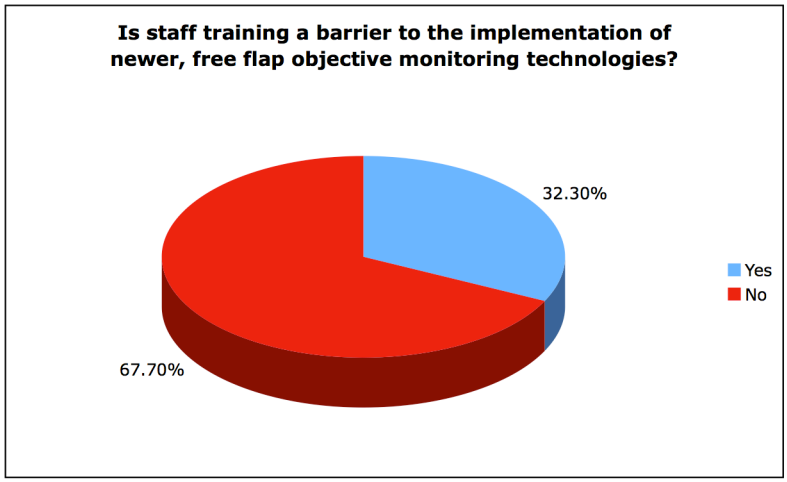

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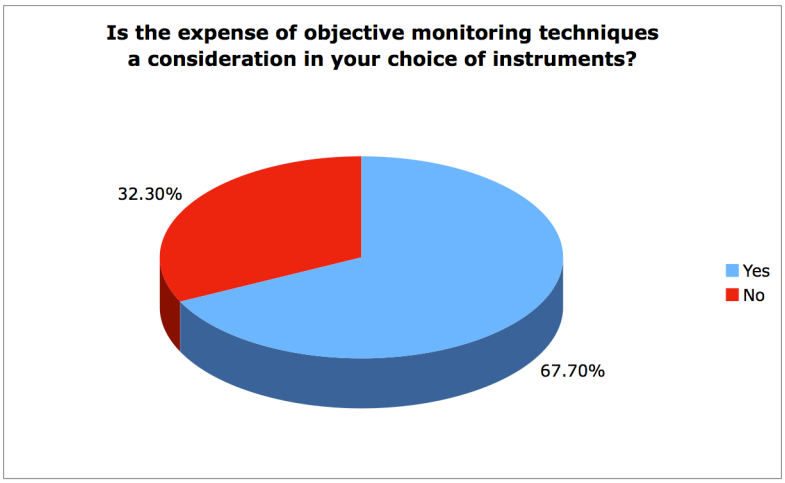

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