Residual Confounding in Observational Studies

To the Editor.—I read the study by Fellahi JL et al. titled “Perioperative use of dobutamine in cardiac surgery and adverse cardiac outcome” with great interest. This study showed that the use of dobutamine was associated with adverse outcomes in adult cardiac surgery, and the authors concluded that these results suggest that dobutamine should only be administered when the benefit is judged to outweigh the risks. Although the study is interesting and the results are provocative, we need to be careful how to examine these results before we conclude that these results suggest that dobutamine may be harmful. First, we can be sure from the data of this observational study that the group of patients who received dobutamine was sicker in both left ventricular function and EURO score. Therefore, it is vital to know whether the propensity score (probability of using dobutamine) was a significant variable in the second method of logistic regression analysis when the propensity score was used as a separate covariate. If propensity score was a significant variable in determining adverse outcome after cardiac surgery in the logistic regression analysis, it would suggest that residual confounding due to “selection bias” caused by using dobutamine in a sicker group of patients was still present, despite the propensity score was used in the multivariate analysis. We definitely need this data to be sure whether any residual confounding was present, and if residual confounding is present, it may at least, in part, explain the results why the use of dobutamine was associated with a poorer outcome. Furthermore, the authors should also discuss the possibility of residual confounding from omitting confounders as a limitation of an observational study. Second, the conclusion of only using dobutamine when benefit is judged to outweigh the risks is not helpful to both practicing anesthesiologists and researchers. The data presented in this study showed that dobutamine was used predominantly in patients with a lower ejection fraction or those with left ventricular dysfunction in their cohort. This practice will remain unchanged in many cardiothoracic centers after knowing the results of this study because this is the group of cardiac patients most likely to have benefits from the use of dobutamine. I believe a more appropriate, balanced, and constructive conclusion from the data of this study is that an adequately powered randomized controlled trial is needed to clarify the risks and benefits of dobutamine in patients with different degrees of left ventricular function in adult cardiac surgery.


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In Reply.—We would like to thank Dr. Ho for his interest in our study. The propensity score used as a covariate in the second logistic regression model (covariance analysis) was not significantly associated with adverse cardiac outcome (P < 0.15), as already mentioned in the footnote of table 4. Regardless of its P value, we disagree with Dr. Ho that a significant propensity score would suggest residual confounding and the reference cited do not support this statement. Dr. Ho is correct when he notes that dobutamine was used predominantly in patients with a lower preoperative ejection fraction. This fact, however, does not necessarily mean that all these patients should have required inotropic support at the termination of cardiopulmonary bypass. The lack of cardiac monitoring to guide inotropic use is a major problem in daily practice, leading to possible inappropriate use of dobutamine for many patients undergoing cardiac surgery. Moreover, both EuroSCORE and left ventricular ejection fraction were relatively well balanced in table 3, which compared baseline characteristics of the subsample after matching groups on the propensity score. We believe that using multiple ways of propensity score adjustment with similar conclusions increases the internal validity of the present work. Of course, we agree with Dr. Ho that unknown confounders can limit the interpretation of any observational study, as we commented in the discussion section of the article, second paragraph.

At last, we would like to clarify an important remark pointed out by John Butterworth, M.D., in the Editorial View that accompanied our article. We have reported the results of a sensitivity analysis after exclusion of “those patients to whom nearly every clinician would administer a positive inotropic drug” with consistent results. We have heard so many clinicians say regarding low doses of dobutamine: “If it does not help, it cannot hurt.” We believe it is high time to change clinical practices and elaborate guidelines for the perioperative use of inotropic agents in cardiac surgery. We also hope our study will stimulate research to confirm or refute our hypothesis-generating data, including replication in other populations. In this line, the results of our study now make the concept of a randomized trial ethically feasible.

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To the Editor— I would like to congratulate Tsuiki and his colleagues on their recent publication examining the upper airway imbalance of airway soft tissue and craniofacial size. They have postulated a causal expansion of excess soft tissue from the maxilla-mandibular enclosure downwards into the submandibular space. This leads to a causal displacement of the hyoid and an increase in the mandibulo-hyoid distance. Previously, some of these authors have focused on an increased submandibular angle leading to difficult tracheal intubation.

Tsuiki’s work is in agreement with Chou and Wu’s work, which proposed that a relatively short mandibular ramus and a caudally positioned hyoid causes a large “hypopharyngeal tongue.” This in turn is associated with both obstructive sleep apnoea and difficult tracheal intubation.

Tsuiki stated that one of the limitations of their study was that it involved only Japanese patients. The study by Lam and workers that is referenced by Tsuiki described a crowded posterior oropharynx and a steep thyromental plane (that is an increased submandibular angle) in Hong Kong Chinese and Caucasians predicts obstructive sleep apnoea though the Chinese group had a higher Mallampatti score, shorter thyromental distance and increased thyromental angle.

Horton and workers in 1990 described a ‘peaddrop’ phenomenon seen with x-ray where the laryngoscope blade causes compression of the tongue and its posteroinferior displacement results in airway obstruction. The epiglottis is also displaced posteriorly against the posterior wall of the pharynx causing difficult tracheal intubation. It would therefore appear that there is a now a link between an anatomical relationship of a low lying hyoid, increased submandibular angle and difficult tracheal intubation.

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References


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In Reply— We thank Dr. Greenland for his thoughtful comments on our article. Difficult intubation is common in obstructive sleep apneic patients and, vice versa, obstructive sleep apnea is common in patients with difficult intubation. He suggests a low hyoid and increased submandibular angle as common anatomical features for both obstructive sleep apnea and difficult tracheal intubation. While we completely agree with the strong linkage between difficult intubation and obstructive sleep apnea, we believe these are independent pathogenic conditions caused by different structural mechanisms.

Certainly, the low lying hyoid per se can result in difficult tracheal intubation, since it impairs an essential step during direct laryngoscopy for improving the laryngeal view, i.e., vertical arrangement of the mandible, tongue base, and larynx to the facial line as we recently reported. In contrast, obstructive sleep apnea can be developed in subjects with normal hyoid bone position. It is of note that hyoid position of apneic patients with large maxillo-mandible size did not differ from that of nonapneic persons as shown in the table 3 of the article. Infants have more collapsible pharyngeal airways than adults although the hyoid bone locates more cranially in infants than adults. Pharyngeal patency is improved by neck extension and impaired by neck flexion, whereas the hyoid bone locates more cranially during neck flexion than during neck extension. The hyoid bone is mobile only in humans; other mammals rarely have obstructive apnea during sleep while obstructive sleep apnea is common in humans, implying possible involvement of mobility of the hyoid bone in pathogenesis of obstructive sleep apnea. However, we do not believe that the low hyoid per se increases pharyngeal collapsibility. Similarly, we consider that increased submandible angle alone contributes little to mechanisms of difficult tracheal intubation, since tracheal intubation is not difficult in most obese patients in whom increased submandible angle is a common feature.

The presence of common anatomical abnormalities does indicate strong linkage between difficult tracheal intubation and obstructive sleep apnea. However, it does not indicate presence of common pathogenesis between them, nor their significant roles in the pathogenesis.

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(accepted for publication October 9, 2008.)
To the Editor.—I applaud the recent landmark investigation by Liang et al.1 regarding nasal mask ventilation. It is a very interesting and innovative work. The abstract was so fabulous that it led me to read the article itself. The points that are not mentioned in the abstract are Bispectral Index monitoring and the number of breaths tried in each trial. Before reading the article, I was even thinking about the depth of anesthesia and its impact on metabolism and carbon dioxide production. After reading, I found out that the brevity of trial time and the use of Bispectral Index exclude the alteration of metabolism. I appreciate their work; I’d like some points to be clarified, though.

What are the criteria of the efficacy in different methods and routes of ventilation? I’d like to know why the researchers have used the term effective while they have worked on airway patency. Shall we use a pressure limiting mode of ventilation first and then use the volume of expired breaths as the end point measurement of the study to represent its efficacy? According to figure 2, the tidal volumes exhaled are much smaller in combined mode than nasal one; this is because of the high airway pressure that exceeds the limiting pressure of 25 cm H2O. When there is no inhalation, how can we expect exhalation? It is quite obvious that the volume of breaths exhaled is a main factor when we measure the volume of exhaled carbon dioxide. In some cases, the authors have used carbon dioxide content even when exhaled tidal volume is near zero; in about half cases, the same carbon dioxide content has been used when the exhaled tidal volume is less than 100 ml. These small volumes are less than anatomical dead space, and in such a condition, nobody expects the above-mentioned carbon dioxide concentration to represent alveoli.

The main aim of this article is to study the patency of airway during anesthesia. Since the above-mentioned researchers have employed tidal volume, carbon dioxide content per breath, and peak inspiratory pressure, they were in search of airway patency and severity of airway resistance. Airway patency can be measured differently. Why not to ventilate in a pressure-cycled mode and measure inspiratory tidal volume? Why not to ventilate in a volume-cycled mode (without pressure limit) and measure peak pressure? Both will represent efficacy of ventilation. Higher tidal volumes in pressure preset and lower peak pressures in volume preset ventilation suggest lower airway resistance and more effective ventilation.

Why not to use other methods of investigating airway patency? Eastwood et al.2 have used pressure-flow relationships of the upper airway (simultaneous measurements of nasopharyngeal, oropharyngeal, and hypopharyngeal pressures) to show increased airway collapsibility during anesthesia. Crawford et al.3 have employed magnetic resonance imaging to measure the dimensions of upper airway in infants during light propofol anesthesia. Nandi et al.4 have been in favor of using conventional lateral radiography to investigate the changes induced by general anesthesia in the upper airway. These are merely some instances, while other methods have also been employed which I hope to be added to the similar future studies.

These researchers have examined their patients in the neutral position that seldom happens in real practice of anesthesia. The study hypothesis is based on overcoming difficult mask ventilation and we are almost sure that when confronting difficulty, the position of head and neck should be modified. For future studies, this study could be repeated in different head and neck positions. In another position, combined mode is probably a better way of ventilation than nasal one. As a result, it seems that it is a little bit soon to decide that “Nasal Ventilation Is More Effective than Combined Oral-Nasal Ventilation.”

A question arises that whether the main locations of obstruction in the airway are the same in inhalation and exhalation or not. Is obstruction possible to happen just during exhalation; or is it less severe during inhalation? I wish the authors had used a measurement of inhaled volume as well to calculate the differences between inhaled and exhaled volumes. By not letting a complete exhalation occur, a new resistance only during exhalation may cause autopeep. Collapsibility of airway is dependent on the balance of compressing and opening forces which are different in inspiration and expiration as well as in spontaneous and mechanical ventilation. For instance, in obstructive sleep apnea, obstruction mainly happens during inspiration which is not the same in mechanical ventilation.

We all have the experience of manual face mask ventilation. At first, we use it simply; and just in the case of difficulty in ventilating, an oral or nasal airway is used; and, at the same time, head and neck position is modified. Suppose that a person is being ventilated only through face mask: the airway is mainly the nasal route and the mouth is closed. If ventilation is helpful and effective, there is no need for oral airway, one of whose characteristics is opening the nasal route by displacing the tongue. Is using nasal mask better than nasal route during face or combined mask ventilation? That is still the question.

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References


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To the Editor:—We read with interest the recent article by Dr. Hunyady and colleagues.1 While we acknowledge that mathematical formulae based on morphometric data may be useful guides, we caution against applying these formulae in lieu of clinical assessment. We conducted a randomized clinical trial to compare three common methods of endotracheal tube (ETT) placement: 1) deliberate mainstem intubation with subsequent withdrawal of the ETT 2 cm above the carina (‘mainstem’ method); 2) alignment of the double black line marker near the ETT tip at the vocal cords (‘marker’ method); or 3) placement of the ETT at a depth determined by the formula: ETT depth (cm) = 3 x ETT size (mmID) + 2 cm (‘formula’ method).2 In our study, the formula method only placed the ETT at the appropriate depth 42%
of the time. In addition, we retrospectively evaluated the efficacy of another formula, ETT depth (cm) = Age(yrs)/2 + 12.1 but appropriate placement would have been achieved only 42% of the time as well. Identification of the carina via auscultation, the mainstem method, was the preferred technique (73%, P = 0.006 vs. the formula method).2

Although our study did not specifically examine the efficacy of the Morgan and Steward formula,4 neither did the study by Hunyady et al.1 The authors’ conclusion that the “… Morgan formula provides good guidance for intubation in children …” is extrapolated based on their measurements and calculations.1 The authors do not specify which technique was used to initially determine ETT depth in their study subjects or report the rates of correct versus incorrect placement for the actual placement methods used. Based on the estimates by Hunyady et al., the Morgan and Steward formula would have placed the ETT tip on average at the 90th percentile for front teeth-to-carina distance and < 0.5 cm from the carina in 13 of their youngest subjects.1 This is concerning since, as the authors astutely point out, the ETT is subject to movement with neck flexion or extension which may result in inadvertent endobronchial ETT placement.5–7

Auscultation methods have their limitations as well,2,5 and no clinical technique results in 100% success. When ETT placement is in question or when accurate ETT depth is mandatory for a particular surgical procedure (i.e., prone position or head and neck surgery), we recommend intraoperative chest radiography, fluoroscopy, or fiberoptic bronchoscopy.

In Reply—We thank Dr. Mariano and colleagues for their comments. As stated in the article, we believe that “sole reliance on a specific formula is not advisable, and careful auscultation is necessary to ensure appropriate position.”1 The stethoscope is indeed a useful, albeit not infallible, tool.

The endotracheal tube (ETT) was positioned according to the preferred method of the attending anesthesiologist. The Morgan formula4 (ETT length at front upper teeth [cm] = 0.10 × height [cm] + 5) was therefore not used in all patients, but the actual ETT tip position was within ±5% of the calculated Morgan formula distance in 138 of the 170 patients. It is correct that we did not test different intubation depth formulas directly, instead we utilized the front teeth-to-carina data to assess whether different intubation formulas would result in bronchial intubation or not. We believe this is a reasonable approach. It is our understanding that Mariano et al. used a similar method to assess the appropriateness of alternative ETT positions in their study.3

We agree with Mariano et al.3 and Phipps et al.4 that the 3 × ETT size formula can be misleading, perhaps because ‘correct’ ETT size varies with tracheal dimensions and depends on whether a cuffed or uncuffed ETT is used. In our patients, three neonates intubated with 3.5 uncuffed ETT’s would have been bronchially intubated if this formula had been applied.

The Morgan formula, on the other hand, is based on the reasonable assumption that the length of the airway tends to increase linearly with the length of the individual. No patient would have been bronchially intubated had the Morgan formula been applied, but thirteen infants and one older child (8%) would have had an ETT tip-to-carina distance of less than 0.5 cm. Although this is less than the 12% noted by Mariano et al. when using the “mainstem method,”3 we share their concern. As mentioned in our paper, it might be helpful to use a modified Morgan formula in infants less than 3 months [ETT length at front upper dental ridge (cm) = 0.10 × height (cm) + 4].3 This does not abolish the risk for low ETT position; one 5-month-old and one 6-year-old in our study would still have had an ETT tip-to-carina distance of less than 0.5 cm had this modification been added. Still, we have found that the ETT position seldom needs to be readjusted when these formulas are applied, and we therefore prefer to first tape the ETT in place and then confirm the position with auscultation.

We rarely use fluoroscopy, chest X-ray, or bronchoscopy to document the ETT position in the operating room. In our experience, intraoperative bronchial intubation is commonly precipitated by a cranial move of the carina, such as occurs during laparoscopic surgery, making such initial documentation less useful.

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To the Editor.—We applaud the endorsement of improving operating room (OR) throughput by a variety of means, including parallel processing. (“Improving OR throughput is not simply a buzzword of the year, but an actual possibility.”) However, we wish to stress that parallel processing does not necessarily require an increase in personnel or additional facilities as stated in the editorial. Indeed, substantial reduction in nonoperative time can be achieved by reallocating responsibilities of the OR staff during the nonoperative interval. Specifically, the circulating nurse can remain in the OR to accelerate the setup for the next case; the anesthesiologist and certified registered nurse anesthetist can divide responsibilities: one may accompany the patient to the recovery area, while the other prepares for the next case; and the housekeeping staff can begin its work after the incision is closed while the patient is still in the OR. Another low-cost solution, based on parallel processing is described by Cendan and Good.

To the Editor.—We read with great interest, “Cardiac Surgery Fast-track Treatment in a Postanesthetic Care Unit” by Dr. Ender et al. Application of this fast-track concept in Leipzig has been met with good results for a wide variety of cardiac surgical patients. Modern perioperative management is faced with the challenge of finding a balance between safe and efficacious results. The objective of fast-track cardiac surgery includes early extubation, reduction of intensive care unit length of stay, and reduction of the total hospital length of stay. This is accomplished with the use of short-acting opioids and hypnotics along with expedited surgical procedures facilitating early extubation after cardiac surgery. In addition the Leipzig fast-track concept avoids intensive care unit admission in selected patients. Similarly, our institution attempts to expedite the management of cardiac patients by using a preanesthetic clinic specialized for day admission cardiac and major vascular surgeries. Day admission surgery is nearly routine in the United States due to desires to decrease costs and resource utilization. Addition of such a preanesthetic clinic to the Leipzig fast-track method would further decrease costs by several mechanisms. Preanesthetic clinics specialized for cardiac and major vascular surgery (thoracic aortic aneurysm) patients are useful to ensure patient safety in a complicated population while avoiding unnecessary expenditures. Furthermore, enhancement of patient satisfaction through-out the surgical process is documented with specialized cardiac perioperative care units. A high-throughput operating room system for joint arthroplasties durably out-performs routine processes. Anesthesiology 2008; 109:25–35

In Reply.—I thank Harders et al. for the comments and pointing out that some of the traditional efforts to improve operating room throughput can be considered to be “parallel processing.” As noted by Harders et al., improving individual functions and improving teamwork has always been essential to improving productivity independent from the actual industry or product, including the operating room. In contrast, the editorial and accompanying article is focused on redesigning the larger process that goes beyond improving individual productivity and teamwork.

Dan C. Krupka is Managing Principal of Twin Peaks Group, LLC, Lexington, Massachusetts, a management consulting firm devoted to patient flow in healthcare. He provided consulting services to MetroHealth Medical Center, Cleveland, Ohio, in 2005 in connection with the project described in the article in Surgery, which is cited in the submitted letter to the editor.

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Innovative Thinking in the Care of Cardiac Surgical Patients

To the Editor.—We read with great interest, “Cardiac Surgery Fast-track Treatment in a Postanesthetic Care Unit” by Dr. Ender et al. Application of this fast-track concept in Leipzig has been met with good results for a wide variety of cardiac surgical patients. Modern perioperative management is faced with the challenge of finding a balance between safe and efficacious results. The objective of fast-track cardiac surgery includes early extubation, reduction of intensive care unit length of stay, and reduction of the total hospital length of stay. This is accomplished with the use of short-acting opioids and hypnotics along with expedited surgical procedures facilitating early extubation after cardiac surgery. In addition the Leipzig fast-track concept avoids intensive care unit admission in selected patients. Similarly, our institution attempts to expedite the management of cardiac patients by using a preanesthetic clinic specialized for day admission cardiac and major vascular surgeries. Day admission surgery is nearly routine in the United States due to desires to decrease costs and resource utilization. Addition of such a preanesthetic clinic to the Leipzig fast-track method would further decrease costs by several mechanisms. Preanesthetic clinics specialized for cardiac and major vascular surgery (thoracic aortic aneurysm) patients are useful to ensure patient safety in a complicated population while avoiding unnecessary expenditures. Furthermore, enhancement of patient satisfaction through-out the surgical process is documented with specialized cardiac preanesthetic clinics. A combination of a specialized preanesthetic clinic and the Leipzig fast-track concept may provide the necessary link in modern cardiovascular perioperative medicine in order to safely decrease costs.

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In Reply:—We appreciate the suggestions that Dr. Silvay has pointed out in his letter to the editor in response to our article about the Leipzig Fast-Track Concept.1 The concept of a preevaluation clinic as described by Dr. Silvay is a powerful tool to optimize safety for the patients and to avoid unnecessary expenditures.2

But one has to differentiate costs incurring for the health system itself and reimbursement of the actual costs for the individual hospital by the health care system. To reduce costs for the individual hospital significantly, one has to look for the real cost driver during the hospital stay of the patient. One of the most intensive cost drivers in each hospital is the intensive care unit.3 With our fast-track concept, we can completely avoid the stay in the intensive care unit for most of the planned fast-track patients. Reimbursement for preclinical evaluation of the patient is not possible for hospitals in the German health care system. The German health care system is based on diagnosis-related groups, a classification of hospital cases expected to have similar hospital resource use.4 Therefore, the hospital gets a fixed fee, for example, for the surgical treatment of aortic valve stenosis, regardless of the actual costs incurred, based on the principle diagnosis, surgical procedure used, age of patient, and expected length of stay in hospital. Preoperative evaluation of the patient is usually performed by the physician, who transfers the patient to the hospital for treatment. Unevaluated diagnostics are performed in the hospital the day prior to surgery after admission to the ward. The admission ward itself is not a cost-intensive unit of the hospital; as long as the patient does not exceed the mean length of stay in the hospital as defined in the diagnosis-related groups, the hospital will save money. However, treatment in a preevaluation clinic, as previously mentioned, is not covered by the diagnosis-related group system. Often we receive patients who have come from a great distance, and hence prior admission to the preevaluation clinic would add to the cost of the hospital. This may be different to the reimbursement practice in the United States.

However, we agree with Dr. Silvay that a combination of a preevaluation clinic and the Leipzig Fast-Track concept will enhance patient satisfaction throughout the surgical process and can lead to further cost reduction for the health care system itself.

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