Update on Cardiac Anesthesia

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Robotic-Assisted Cardiac Surgery: Alive and Well, Dead, or Ailing?

There has been much ado about minimally invasive cardiac surgery, yet its appeal remains insufficient to extract cardiac patients from the clutches of invasive cardiologists and back to cardiac surgeons. Although minimally invasive cardiac surgical techniques have been available in some form since the 1970s, interest among cardiac surgeons has flourished mainly since the mid-1990s, yet many cardiac surgeons appear to remain unimpressed. What have we learned about these techniques over the past decade? First, we know that one can do coronary artery bypass grafting (CABG) very well without cardiopulmonary bypass (CPB) with less bleeding, transfusion, strokes, length of hospital stay, and possibly renal failure. Most of these differences have been sufficiently unimpressive, however, that off-pump CABG (OPCAB) has only slightly reduced but not replaced the traditional CPB approach to CABG (CCAB). Coronary stents have had a greater impact than OPCAB by a substantial margin.

In recent years interest has turned to robotic-assisted cardiac surgery in various forms. Initially used principally to harvest internal thoracic arteries for single vessel LAD CABG, additional robotic applications have emerged. The natural robotic coronary revascularization progression for a cardiac surgeon goes something like this: robot-assisted isolated left internal mammary artery (LIMA) harvest with off-pump single-vessel LAD CABG via mini-anterior thoracotomy, robot-assisted LIMA harvest with robot-assisted single LAD anastomosis using Port-access CPB (commonly called totally endoscopic CABG, or TECAB), robot-assisted LIMA and right IMA harvest with robot-assisted 2-vessel coronary anastomosis using minimally invasive CPB, and finally robot-assisted off-pump CABG using coronary stabilizers applied via portholes (Argenziano 2006, de Canniere 2007, Casula 2004, Srivastata 2006). Relatively few surgeons "survive" this entire progression of technical experience and difficulty, and many have not even embraced the first step. In part, this may be attributable to the $1M initial capital cost of the robotic system, but many surgeons simply seem disinterested in pursuing robotic cardiac surgery as yet. Clearly these techniques are more technically demanding than traditional cardiac surgery

The Da Vinci device has been the dominant robot for cardiac surgery. This device permits the surgeon to sit across the operating room from the patient and operate with robotic hands using "virtual reality" 3-D visualization. The remote "hands" permit movement with six degrees of freedom that can even reduce human tremor. There is a slight but perceptible delay between surgeon hand movement and robotic instrument action on the surgical field, and the device to date lacks tactile feedback about tissue resistance or grip strength (Kypson 2006, 2007). Another robotic device (AESOP) offers voice-activated camera movement, but lacks the 3-dimensional visualization and degrees of freedom of the DaVinci robot.

Several reports have shown mortality, morbidity, and graft patency results approaching or equaling those for CCAB (Bonatti 2004, Argenziano 2006). Operative times tend to be longer, especially early on in a surgeon's learning curve. Hospital stay tends to be shorter than that for CCAB or non-robotic OPCAB. Robotic off-pump CABG boasts hospital discharge as early as 24 hours postoperatively (Subramanian 2005). The latter approach has been recently enabled by continued refinement and miniaturization of coronary stabilizing devices and greatly facilitated by the still-experimental use of staple-like Nitinol suture substitutes for coronary anastomoses. Some enthusiasm has developed for a hybrid approach, in which percutaneous coronary stenting accompanies off-pump or on-pump TECAB to the left anterior descending coronary artery (Katz 2006). The stenting can occur either simultaneously with TECAB or on a different day. Hybrid operating/Interventional radiology rooms are springing up around the country to facilitate this approach, but as yet there is little information about outcomes or the frequency with which this approach is used. Katz et al. reported disappointing 3-month patency rates (67%) for the stent portion of this combined revascularization approach (Katz 2006).

Other procedures that have proven amenable to robotic assistance include mitral valve repairs and replacements, atrial septal defect closures, and MAZE procedures for atrial fibrillation. Mitral valve repairs and replacements have most often been performed with a small right thoracotomy plus 3-5 portholes for various purposes. The overly optimistic term “totally endoscopic” has been used to describe this procedure even though a small thoracotomy with rib spreading is used (Felger 2001). Results have been generally favorable when using this approach in combination with minimally invasive CPB (Folliguet 2006, Tatooles 2004). Early improvements in mitral regurgitation have been mostly comparable to those with median sternotomy and hospital discharges have been quicker, but prospective randomized trials are lacking. Robotic MAZE procedures can be performed with or without CPB. Some surgeons favor CPB because of the smaller heart size and the ability to enter the left atrium, perhaps leading to a more complete ablation with superior freedom from atrial fibrillation recurrence.

As promising as robotic heart surgery may be, it has its detractors. Morgan et al. note that cost savings from shorter lengths of stay are easily offset by the cost of the robot for quite some time, arguably for the life expectancy of the robotic device (Morgan 2005). Jacobs et al. used a mechanical model to demonstrate lesser accuracy of instrument movements as compared to manual touch movements when the model’s movement simulated that of a beating heart (Jacobs 2003). Robiscek wrote a scathing 2008 editorial suggesting, among other things, that robotics succeed in combining the “clinically dubious with the technically overcomplicated.” (Robiscek 2008) He provides results from a 2005 survey indicating that, of 56 institutions having robots in active use for cardiac surgery, only 7 were using these devices for over 50 cardiac procedures per year, while 30% were using it for 1-5 procedures per year. He opined that hospital administrators have discovered that the best way to make a robot cost-effective is to find a robotically-proficient urologist to perform robot-assisted prostatectomies, because this application offers the best potential for cost-effective clinical volumes, reasonable operative times, and shortened hospital stays. In conclusion, robotic-assisted cardiac surgery is alive but ailing, although its potential for recovery and growth seems strong.

Anesthetic implications: These vary with the procedure, but some generalities hold. Almost all robotic cardiac procedures virtually require a double-lumen tube with sustained periods of one-lung ventilation. Even with one-lung ventilation, mediastinal movement can impair the surgeon’s vision and technical facility, hence he or she may request low tidal volumes or intermittent apnea especially when working on the beating heart or when harvesting the right IMA from robotic ports placed through the left hemithorax. Most often some form of CPB is used. In some cases, CPB venous cannulation is via the right internal jugular vein, hence central venous access must use another site such as a subclavian vein or the left internal jugular vein. Virtually all robotic procedures should use transcutaneous defibrillator pads. If the off-pump approach is used, some prefer a “second-skin” type of circulating water device to prevent hypothermia, and this approach does seem superior to traditional forced-air heaters. I am aware of some thermal injuries from these devices, however, so caution is advised. Transesophageal echocardiography (TEE) is helpful for all and essential for some robotic operations (e.g., ASD repair, mitral valve repairs). For minimally invasive CPB, TEE is critical for assessment of venous cannula positioning, retrograde cardioplegia cannula position (if used), and intra-aortic balloon occlusion device positioning (if used). Most centers report routine use of PA catheters; in some cases a single-lumen PA “drain” is placed by the anesthesiologist to function as an indirect left atrial drainage catheter. Fast-track anesthesia with early extubation appears to be the norm, which can involve either extubation immediately at the conclusion of surgery or within a few hours of arrival in the ICU. Postoperative analgesic considerations are similar to those for comparable non-robotic operations such as video-assisted thoracotomy or lobectomy, although few anesthesiologists opt for neuraxial analgesic techniques if CPB is used.

Heparin: Old Drug, New Problem

Aside from morphine, heparin may be the oldest drug regularly used by anesthesiologists. Since heparin has been used daily in thousands of surgical procedures for decades, it comes as a surprise that heparin has recently been associated with hypotensive reactions consistent with life-threatening anaphylactic or anaphylactoid reactions. The only unsurprising thing about this is that heparin is the “dirtiest” drug in our pharmacopoeia in that it is purified mostly from pig intestines. Even with perfect purification, it always has minor contaminants, and typical unfractionated heparin contains an impressive range of polysachharide chain lengths. Hence, if one were to make an educated guess about a drugs most likely to contain clinically significant contaminants, heparin would top the list.

In January, 2008, the Centers for Disease Control received a report from Missouri about allergic-type reactions in pediatric dialysis patients occurring on or after November 19, 2007 (MMWR Morbidity and Mortality Weekly Report, Feb 8, 2008). This prompted an investigation which uncovered approximately 65 similar reactions in 53 hemodialysis patients in twelve states. 81 fatalities have been possibly related to this phenomenon (Kishimoto 2008). CDC established a working definition of these reactions, which required at least two of the following signs and symptoms: generalized or localized sensation of warmth, numbness or tingling of extremities, difficulty swallowing, dyspnea/wheezing/chest tightness, low blood pressure/tachycardia, or nausea/vomiting. The common factor among these reactions was heparin 1,000 units/mL manufactured by Baxter, Inc, mostly or solely from a single lot or batch. Baxter subsequently recalled nine lots of heparin. Some cases of possible anaphylactoid reactions during cardiac surgical procedures were also brought to the attention of Baxter and the Food and Drug Administration (FDA 2008). The Baxter recall appeared to have solved this problem, yet in March, 2008 a heparin recall was announced in Germany as a result of a cluster of similar reactions in dialysis patients who received heparin from a different manufacturer. Heparin has historically had a very low rate of anaphylactic or anaphylactoid reactions, and has at times been used to attenuate or prevent such reactions. Heparin does normally decrease systemic vascular resistance 10-20% (Seltzer 1979), but larger decreases should invoke suspicion of an anaphylactoid reaction or an alternative cause.

Chemical analysis of the suspect drug lot pointed to heparin manufactured in a Baxter plant in Changzhou, China (Hughes 2008). The contaminant appears to be a compound called oversulfated chondroitin sulfate (OSCS). Although chondroitin coexists in vivo with heparin and is removed by the heparin purification process, OSCS is not a naturally occurring chondroitin, so it was most likely introduced artificially. OSCS directly activates the kinin-kallikrein pathway in humans (Kishimoto 2008, Guerrini 2008), whereas heparin (and apparently normally sulfated chondroitin) does not (Pixley 1991). This in turn leads to generation of C3a and C5a, which are potent anaphylatoxins. Patients taking angiotensin converting enzyme inhibitors (ACEIs) could be especially susceptible to such reactions, since ACEIs inhibit bradykinin breakdown. An apparent explanation has been offered for the deliberate introduction of this contaminant: it can be produced more cheaply and its anticoagulant effects mimic heparin's such that the usual heparin potency clotting assays would not detect it (Hughes 2008). In March the FDA posted a newly required procedure to rule out this contaminant in all unfractionated heparin products prior to their release. This procedure involves capillary electrophoresis and proton nuclear magnetic resonance. (FDA 2008).

This frightening contamination of unfractionated heparin has captured the attention of the public and of Congress, such that both the FDA and drug manufacturers have come under intense scrutiny for quality control in the manufacture of drugs. The vast majority of commercial drugs sold in the United States are manufactured outside the U.S. FDA bears official responsibility for inspecting overseas manufacturing plants, but it does not appear that sufficient funds are available for FDA to effectively carry out this charge. It is questionable whether a routine inspection would have uncovered this apparent heparin sabotage anyway. Drug manufacturers bear responsibility as well, since they are legally accountable for their products and have chosen to manufacture most drugs overseas. It remains unclear what changes may transpire in the manufacture and testing of drugs manufactured overseas that are sold in the U.S., so major adverse reactions or complications from drug impurities could also occur with other drugs. Fortunately, it appears that heparin safety has returned to its pre-2007 state, although anesthesiologists should remain wary and should contact FDA about any events suspicious for heparin-induced anaphylactoid reactions.

To digress slightly, this occurrence begs the question of why we still use a drug as ancient and imperfect as heparin. Heparin is a reliable but incomplete anticoagulant, and it undesirably activates platelets. Direct thrombin inhibitors (DTIs) such as bivalirudin, hirudin, and argatroban better inhibit thrombin and lack both platelet activation and thrombocytopenia as complications. In addition, they have shorter clinical half-lives than heparin. Although DTIs offer much promise in nonsurgical applications and possibly even in off-pump cardiac or vascular surgical procedures, the lack of an immediately effective neutralizing agent imposes sufficient bleeding in the first few hours after CPB that DTIs cannot routinely be recommended for CPB anticoagulation. After 55 years of use for CPB, heparin unfortunately remains the best anticoagulant for that clinical setting.

Central Venous Catheter (CVC) Placement with Ultrasound: Boon or Bane?

Let's cut to the chase: it's a boon. But is it such a boon that failure to use real-time ultrasound for every CVC placement should be considered heretical? Things seem to be moving in the direction of real-time ultrasound as a standard of care. Does the available evidence justify such a draconian approach? Let's examine the evidence.

Use of Doppler ultrasound (identifying the vein via its characteristic audible "hum") to localize the internal jugular vein was reported as early as 1978 (Ullman 1978). In 1991 Troianos et al. reported the use of B-mode (2D) ultrasound (BUS) to depict the anatomy of the right internal jugular vein (RIJ) (Troianos 1991). In a teaching hospital Troianos et al found that the use of ultrasound-guided RIJ puncture decreased the number of needle passes and the average time taken per cannulation. There was also an impressive trend toward a decrease in the incidence of arterial punctures (7 of 83 patients with standard approach, 1 of 77 with ultrasound). Since this important study, there have been numerous others comparing various aspects of ultrasound-guided RIJ cannulation to the traditional "landmarks" anatomic approach. Conditions of study and patient populations have varied considerably. Unsurprisingly, Schummer et al. showed a higher first-needle pass success rate using B-mode than Doppler ultrasound to locate the RIJ (Schummer 2006), so studies cited henceforth will be limited to B-mode ultrasound technique. Keenan reviewed the literature in 2002 (Keenan 2002), at which time he found 12 prospective studies comparing ultrasound to the anatomic landmark-based technique (LM) for RIJ cannulation in adults, but only 4 trials were clearly conducted on consecutive patients. Six of those studies compared BUS to LM techniques, but only the Troianos study routinely involved anesthesiologists or cardiac surgery patients, and five used supervised residents or fellows as the primary operators. Only the studies of Denys et al. (N=604) and Troianos et al. (N=160) investigated more than 100 patients (Denys 1993, Troianos 1991). Some aspects of Keenan's pooling of data are questionable, in that he combined adult and pediatric trials as well as Doppler and B-mode ultrasound trials. Nevertheless, ultrasound consistently reduced the number of needle passes required for initial venous blood "flash," and cannulation failure rates. With respect to the time taken for IJ cannulation, various studies favored either BUS, LM, or neither technique. Only the study of Denys et al. found a statistically significant difference in arterial puncture rate (BUS 8/302, LM 25/302). A 2003 meta-analysis by Hind et al. (Hind 2003) had similar findings to those of Keenan, and also indicated that the data on the use of US vs LM techniques for cannulation of the subclavian or femoral veins in adults were inconclusive. With one exception (Karakitsos 2006), studies to date lack comparative analysis of outcomes such as central-venous catheter sepsis, pneumothorax, and clinically significant cervical hematomas for BUS versus LM IJ cannulation techniques. Stroke, mortality, and cost-effectiveness comparisons are either nonexistent or inconclusive.

Several additional studies have been published since 2003. In a retrospective study of 484 IJ cannulations performed in an ICU mostly by junior residents supervised by senior residents, Martin et al. found no significant difference in complications between BUS and LM techniques (Martin 2004). In a study where radiologists randomly used BUS and fluoroscopy to place emergency IJ dialysis catheters, Koroglu et al. needed fewer needle passes with BUS and significantly reduced the arterial puncture rate from 35% (!) with LM to 0% with BUS (Koroglu 2006). This suggests that radiologists are highly skilled with imaging techniques and very unskilled with "blind" anatomic techniques. Using emergency room attending physicians or residents for IJ cannulation in 130 patients, Leung et al. achieved higher first-pass success with BUS than LM, with a carotid puncture rate of 4/65 using LM and 1/65 using BUS (apparently NS, but overall complications were significantly reduced with BUS) (Leung 2006). Milling et al. randomly assigned 201 emergency room patients to either real-time BUS, static BUS (i.e., scan and mark IJ location prior to attempted puncture), or LM technique, and found that first-pass success, overall success, and time for cannulation were best with real-time BUS, next best with static BUS, and worst with LM (Milling 2005). There were 8 carotid punctures using LM and 2 each with real-time and static BUS (difference not significant). In 2006 Karakitsos et al. uniquely used attending physicians (cardiologists, intensivists, and surgeons) exclusively in a randomized, prospective study of 900 intensive care patients (Karakitsos 2006). BUS was superior to LM (top of the sternocleidomastoid triangle, ipsilateral nipple needle trajectory) in overall success in cannulation, number of attempts required for cannulation, carotid artery puncture, hematoma formation, pneumothorax rate, and catheter-associated blood stream infection. In a teaching hospital using predominantly first- and second-year anesthesiology residents to perform IJ cannulations, Augoustides et al. found that both needle-guided BUS and non-needle-guided BUS resulted in a 4-5% carotid puncture rate without clinically important sequelae (Augoustides 2005).

Most studies comparing BUS to LM techniques have noteworthy limitations. First, the LM technique commonly either varies within the same study or is inadequately described. This aspect and the lack of clear consensus about the best LM technique to minimize needle passes, failed cannulation, and arterial puncture place the LM technique at a disadvantage in most comparisons. Second, most studies used trainees predominantly or exclusively, and some studies show that the advantage of BUS over LM is accentuated by operator inexperience. Third, some studies showing BUS superiority had unacceptably high arterial puncture rates with the LM technique. Over a period of decades, the LM technique has most often produced an arterial puncture rates of 5% or less (even with trainees), so arterial puncture rates exceeding 10% suggest operator inadequacy with the LM technique. Further, although carotid puncture is clearly undesirable, most do not result in clinically significant complications. Fourth. the absence (to date) of biplanar or 3D scanning for IJ puncture places the BUS operator at some disadvantage, because transverse (coronal plane) scanning may fail to identify the needle tip and longitudinal (saggital plane) scanning most often fails to simultaneously image the carotid artery and the IJ vein. Finally, no study has compared BUS to LM when IJ cannulations were exclusively performed by anesthesiologists who had completed residency training. As a corollary, there is insufficient evidence to make a reliable recommendation about the merits of static precannulation anatomic assessment of the IJ/carotid anatomy to those of real-time scanning using experienced operators for both techniques. Although I do not wish to cast aspersions upon our colleagues in emergency medicine, critical care, radiology, and cardiology, it is likely that the LM technique would enjoy greater success among attending anesthesiologists because of frequent performance of and cumulative experience with that procedure. Even among anesthesiologists, it seems likely that those who most often anesthetize patients for cardiothoracic and major intra-abdominal procedures (or regularly in the ICU) would perform the LM technique most often and with greatest success. As an analogy, it would be difficult to imagine establishment of standards for a surgical approach to Cesarean section if those standards were primarily based on the published experiences and complication rates of residents, family practitioners, and midwives.

Nevertheless, much has been learned from BUS studies of IJ cannulation, to wit,

1. Anatomic variations on the position of the IJ relative to the carotid artery are surprisingly frequent and often frightening,
2. The RIJ can be either so small or so clotted as to warrant a first cannulation attempt elsewhere.
3. The less one rotates the head away from the side of intended IJ cannulation, the less the IJ overlaps the carotid artery.
4. The IJ is extremely compressible, to the extent that it may be difficult to avoid so-called double-wall IJ penetration with absence of blood “flash” until the needle is slowly withdrawn (even if it was slowly advanced). When the IJ predominantly lies anterior to the carotid artery, this becomes especially worrisome, and suggests the need for either an alternative site (left IJ or subclavian vein) or an alternative needle trajectory (e.g., medial-to-lateral).
5. Unsurprisingly, Trendelenberg’s position and the ValSalva maneuver substantially increase the diameter of the IJ without affecting the diameter of the carotid artery.

To what degree are anesthesiologists embracing the use of ultrasound for IJ cannulation? Bailey et al. surveyed cardiothoracic anesthesiologists in 2006, and found that two thirds of respondents never or almost never used ultrasound for IJ cannulations (Bailey 2007). In a survey of United Kingdom pediatric anesthesiologists, Tovey and Stokes found that only 26% of pediatric anesthesiologists always used ultrasound for IJ cannulation (Tovey 2006). These findings are interesting in view of recent recommendations. In a 2003 review article in the New England Journal of Medicine, McGee and Gould recommended that ultrasound guidance be routinely considered for IJ cannulations (McGee 2003). In 2007 Feller-Kopman recommended that chest physicians and intensivists “embrace the broad clinical applications of ultrasound,” stopping just short of recommending its routine use for IJ cannulation (Feller-Kopman 2007). In 2002, the British National Institute for Clinical Excellence recommended 2-D imaging as the preferred method for insertion of IJ central venous catheters in adults and children in elective situations. On the North American side of the “pond,” in 2001 the Agency for Healthcare Research and Quality recommended the use of ultrasound for central venous cannulation as one of 11 practices to improve patient care. Therefore, despite substantive limitations in the quality of the scientific literature, regulatory and safety advisory agencies have boarded the ultrasound bandwagon on the subject of central venous cannulation.

Conclusion: Despite the absence of sufficient well-designed comparison studies of BUS and LM techniques in the hands of ideally experienced operators, it seems reasonable to require that B-mode ultrasound be available in all anesthesiology settings where central venous cannulation is frequently performed. For elective IJ cannulations, it also seems reasonable to expect that attempts be made to scan the anatomy of the IJ and carotid artery either immediately before (static) or during (dynamic, real-time) cannulation. Should existing ultrasound device(s) currently be in use elsewhere or should the need for central venous cannulation be urgent or emergent, the practitioner should use his or her own judgment about whether to proceed with a LM technique or await the availability of an ultrasound device. When the LM technique is used, strong consideration should be given to “crossing over” to real-time BUS if more than two needle passes are required to identify the IJ vein. Because of soft clinical outcomes, low numbers of patients, and suboptimal study design in most comparison studies to date, I do not believe it is appropriate to mandate the use of ultrasound for IJ cannulation as a minimum standard of care at this time. I say this despite my personal preference for its routine use.

References (alphabetically by section)

Minimally invasive surgery/Robotics
Argenziano M. Ann Thorac Surg 2006;81:1666-75
Bonnatti J. J Thorac Cardiovasc Surg 2004;127:504-10
Casula R. Int J Medical Robotics and Computer Assisted Surgery 2004;1:98-106
de Canniere D. J Thorac Cardiovasc Surg 2007;134:710-16
Felger JE. Ann Thorac Surg 2001;72:1203-9
Folliguet T. Eur J. Cardio-thoracic Surgery 2006;362-6
Jacobs S. Ann Thorac Surg 2003;76:2029-36
Katz MR. Circulation 2006;114:I-473-I-476
Kypson AP. Expert Rev Med Devices 2006;3:335-43
Kypson AP. Cardiology 2007;107:147-5
Morgan JA. J Card Surg 2005;20:246-51
Robicsek F. J Thorac Cardiovasc Surg 2008;135:243-6
Srivastava S. Ann Thorac Surg 2006;81:800-6
Subramanian VA. Ann Thorac Surg 2005;79:1590-6
Tatooles A. Ann Thorac Surg 2004;77:1978-84

Heparin
Guerrini M. Nature Biotechnology 23 April 2008;doi:10.1038/nbt1407:1-7 (Advance online publication)
Hughes S. Heartwire 2008, copyright 2008 Medscape, http://www.medscape.com/viewarticle/573789, pp 1-2
Kishimoto TK, NEJM April 23, 2008, http://content.nejm.org/cgi/content/full/NEJMoa0803200, pp 1-13
MMWR: Morbidity and Mortality Weekly Report, Centers for Disease Control and Prevention (CDC) 2008;57(5):124-5
Pixley RA. Thrombosis and Haemostasis (Stuttgart) 1991;66:540-7
Seltzer JL. Acta Anaesthesiol Scand 1979;23:575-8
US Food and Drug Administration, 2008, http://www.fda.gov/cder/drug/infopage/heparin/default.htm

CVP Ultrasound
Agency for Healthcare Research and Quality. Making health care safer: A critical analysis of patient safety practices. 2001. Available at http://www.ahrq.gov/clinic/ptsafety/chap21.htm
Augoustides JG. J Cardiothorac Vasc Anes 2005;19:310-15
Bailey PL. Anesth Analg 2007;104:491-7
Denys BG. Circulation 1993;87:1557-62
Feller-Kopman. Chest 2007;132:302-9
Hind D. BMJ 2003;327:361-4
Karakitsos D. Critical Care 2006;10:R162(doi:10.1186/cc5101)
Keenan SP. J Critical Care 2002;17:126-37
Koroglu M. Acta Radiologica 2006;47:43-7
Leung J. Ann Emerg Med 2006;48:540-7
Martin MJ. Current Surgery 2004;61:71-4
McGee DC. NEJM 2003;348:1123-33
Milling TJ. Crit Care Med 2005;33:1764-9
National Institute for Clinical Excellence, Guidance on the use of ultrasound locating devices for placing central venous catheters. www.nice.org.uk, Issue date Sept, 2002, Review date Aug, 2005
Schummer W. J Clin Anesth 2006;18, May issue, accessed via MDConsult
Tovey G. Eur J Anaesthesiology 2007;24:71-5
Troianos CA. Anesth Analg 1991;72:823-6
Ullman JL. Anesth Analg 1978;57:118