Dynamic left ventricular outflow tract obstruction can cause refractory shock in ICU patients.

**Background:** Dynamic left ventricular outflow tract obstruction (LVOTO) is a well recognized feature of hypertrophic cardiomyopathy. That dynamic LVOTO can occur outside of the setting of hypertrophic cardiomyopathy and can be the cause of refractory hypotension in the critical care setting may not be as well recognized. With hypertrophic cardiomyopathy, dynamic left ventricular obstruction occurs as systole progresses and the anterior mitral leaflet is drawn toward the hypertrophied based ventricular septum. This results in subaortic stenosis impeding left ventricular output. Dynamic LVOTO can be found in patients without hypertrophic cardiomyopathy. The settings in which this can occur typically involve the presence of left ventricular hypertrophy and increased cardiac contractility.

**Objective:** To describe cases in an ICU setting in which LVOTO occurs.

**Design:** Case reports.

**Participants:** 5 patients who developed LVOTO while being treated in the ICU.

**Methods:** None of the patients had hypertrophic cardiomyopathy, and all were women (age range, 50 to 70 years) who had a prior history of hypertension.

**Results:** Symptoms at time of presentation included chest pain, dyspnea, fatigue, and dizziness. Systolic ejection murmur was noted in 4 of 5 patients. Echocardiography (ECG) revealed ST and T wave changes. Three of the 5 patients were hypotensive. The presence of LVOTO was confirmed by echocardiography or cardiac catheterization in these patients.

**Conclusions:** Dynamic LVOTO is an underappreciated entity that can occur in ICU patients, and can result in hypotension that will not respond to inotropic agents, and indeed worsen when inotropic agents are added. LVOTO occurring in the absence of hypertrophic cardiomyopathy can be diagnosed by ECG.

**Reviewer’s Comments:** It is important not to miss the diagnosis of LVOTO in the critically ill hypotensive patient, as their management will be different. In the hypotensive patient with LVOTO, continued use and reliance on inotropic agents (such as dobutamine or dopamine) may not be prudent. Beta-blockers can be utilized to reduce the left ventricular outflow tract gradient. It is mandatory to restore intravascular volume. The use of an alpha agonist, such as phenylephrine, may be helpful. (Reviewer-Richard A. Nusser, MD).

© 2009, Oakstone Medical Publishing

Keywords: Unexplained Hypotension

Print Tag: Refer to original journal article
DNA methylation decreases in people exposed to air pollution potentially presenting a mechanism for causing long-term chronic illnesses.

**Objective:** To determine whether there is a correlation between blood DNA methylation and air pollution.

**Participants/Methods:** Patients were all elderly individuals with an average age of 73 years; they were admitted in the study between January 1999 and June 2007 as part of an aging study. All subjects had to be evaluated with a medical examination every 3 to 5 years at which time a blood sample was collected. Ambient air pollution indices were collected for particulate matter 2.5 microns and particulate matter 10.0 (black carbon) as well as others. Various time windows of exposure for evaluation were taken from 4 hours before a blood draw to 7 days after a blood draw. Standard techniques were used for measuring DNA methylation.

**Results:** Methylation was lowest in blood DNA taken on Mondays and highest on Wednesdays. They were also highest in spring and lowest in the fall. Methylation decreased in relation to black carbon exposure and particulate matter 2.5 levels. Using 7-day moving averages, the authors were able to show an independent effect of black carbon on methylation with a dropout of the relationship between particular matter 2.5 and methylation. This suggested that there was a time varying component to methylation. Once a 7-day moving average was used for the analysis, the day of the week and the season became unassociated with methylation.

**Conclusions:** The authors concluded that there was a decrease in DNA methylation after exposure to traffic toxins. There is the question of whether in fact this is the mechanism behind the increased risk for cardiovascular disease associated with exposure to traffic pollution.

**Reviewer's Comments:** It would appear that we are very rapidly honing in on the potential mechanism between air pollution and poor outcomes not just in cardiovascular disease, but in other diseases as well. It would appear that the body's response to air pollution is a reduction in methylation allowing for the progression of certain aspects of heart disease, such as atherosclerosis and oxidative stress. It is probable but not yet proven that these mechanisms may also be associated with the progression of asthma and COPD in areas of high pollution. Honestly, further investigation is necessary; however, it still raises a very significant red flag in that patients with significant heart disease or lung disease should try to limit their exposure to traffic pollution. (Reviewer-Eric H. Gluck, MD, JD).

© 2009, Oakstone Medical Publishing

Keywords: Pollution

Print Tag: Refer to original journal article
Patients with COPD tend to inhale more frequently following swallowing than control subjects do; this might result in increased risk for aspiration.

**Objective:** To evaluate the relationship between breathing and swallowing in patients with chronic obstructive pulmonary disease (COPD).

**Participants/Methods:** COPD patients were recruited from the home oxygen program at a Veteran's Affairs hospital in Pittsburgh. Standard definitions for COPD based on pulmonary function testing were employed. Patients with known neurological diseases that could cause swallowing difficulties were also excluded. Twenty-five subjects were eventually identified who had an average age of 69 years. All of the participants were male. Patients answered a questionnaire created to identify patients with dysphagia. The KayPentax Swallowing Station and Swallowing Signals Lab from Lincoln, New Jersey, allow the acquisition of simultaneous recording of respiratory pattern and a surface electromyogram. This allows for the determination of when in the respiratory cycle swallowing is initiated. In addition, an inductance plethysmography machine was used to follow respirations. The data were then simultaneously recorded and age-matched controls were obtained.

**Results:** Both groups swallowed 250 pudding swallows and 225 cookie swallows. Data demonstrated that in COPD patients, the solid bolus was swallowed during inhalation significantly more often than in control subjects. This was true for the semi-solid swallows as well in COPD patients. Healthy subjects swallowed significantly less frequently during inhalation when eating the cookie than when eating the semi-solid. Postswallowing inhalation occurred significantly more often in the COPD group when eating the semi-solid compared to control subjects. Subjects with COPD swallowed the pudding at low tidal volume significantly more often than swallowing cookie. In contrast, control subjects did just the opposite.

**Conclusions:** The authors concluded that patients with COPD do exhibit disruptive coordination of the ventilatory cycle with swallowing. The increase amount of inhalation preceding and after swallowing might increase the risk of aspiration, and this in turn might be a risk factor for exacerbations.

**Reviewer’s Comments:** This study is very interesting since it sheds light on a subject about which most people do not think. Patients with abnormal ventilatory cycles will also have difficulties in the ability to eat. The authors stressed the possibility of aspiration, with the aspirations leading to possible exacerbations of COPD, but I wonder whether this difficulty in eating and breathing might also be one of the reasons that patients with COPD have a tendency to become malnourished. (Reviewer-Eric H. Gluck, MD, JD).

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Keywords: Breathing/Swallowing

Print Tag: Refer to original journal article
DE Not Always Accurate in Predicting PA Pressures

Accuracy of the Doppler Echocardiography in the Hemodynamic Assessment of Pulmonary Hypertension.

Fisher MR, Forfla PR, et al:

Am J Respir Crit Care Med 2009; 179 (April 1): 615-621

DE frequently over- and underestimates pulmonary artery pressure, sometimes by enough to create false positives and false negatives.

Objective: To prospectively evaluate the accuracy of Doppler echocardiography (DE) in determining pulmonary artery systolic pressure.

Participants/Methods: The study was performed at Johns Hopkins University. Consecutive patients who underwent a right heart catheterization for the diagnosis and/or management of pulmonary hypertension (PH) are included as the cohort for this study. Standard techniques were used for doing the right heart catheterization, and standard measurements were obtained. All patients then underwent a comprehensive 2-dimensional study of the heart using transthoracic echocardiography. Standard techniques for interpreting the Doppler waves and size of the atrium and ventricles were employed. Standard equations were used for the calculation of pulmonary artery pressure. The cohort was comprised of 75 consecutive patients seen between March and October of 2004.

Results: Only 1 patient could not have adequate data obtained from the echocardiogram. The average age of the patients was 54 years, with a preponderance of females. Most of the patients had primary pulmonary hypertension (PPH), but there were groups with secondary PH related to interstitial lung disease, venous hypertension, and obstructive sleep apnea. Six patients did not have any appreciable tricuspid regurgitation. Four of these patients did have evidence of PH by catheterization. The correlation coefficient for the Doppler study compared to pulmonary artery catheterization was 0.66. There was a slight bias, with the Doppler study underestimating pulmonary artery pressure. Forty percent of the echocardiographic estimates were accurate if one used a measurement within 10 mm of the actual catheterization value. Overestimation and underestimation of pulmonary artery pressure occurred with a similar rate. However, the magnitude of the underestimation was slightly greater than the overestimation of the magnitude.

Conclusions: DE might frequently be inaccurate in estimating pulmonary artery pressure and cardiac output in patients being evaluated for PH.

Reviewer's Comments: Based on the other data we have recently reported, I am not surprised by the results of this study. The estimation of pulmonary artery pressure using indirect means is fraught with difficulties because of the variability in the geometry of the hearts and the variability in the creation of tricuspid regurgitation by elevated right ventricular pressures. I still get the feeling that this technique is useful as a first-line screening tool with the proviso that there is a possibility that a negative result may still mean that the patient has PH and a positive result still can mean that the patient does not. (Reviewer-Eric H. Gluck, MD, JD).

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Keywords: Diagnostics

Print Tag: Refer to original journal article
A new TB has demonstrated the ability to develop antibodies in patients with latent TB without worsening infiltrates on CT.

**Objective:** To determine immunogenicity and safety of a new vaccine for tuberculosis (TB).

**Participants/Methods:** Individuals were enrolled in the study if they knew they had been exposed to TB and had a positive reaction to immunogenicity testing. No patients with active disease were enrolled. Patients underwent an interferon (IFN)-gamma spot assay to determine whether they were infected with TB using 2 different specific antigens. All patients were negative for evaluation for HIV, hepatitis B, and hepatitis C and all had a normal blood count, renal function, and liver function tests. After vaccination, patients were followed for at least 12 months with blood samples evaluating the presence of inflammatory markers, as well as immunological assays. Also, patients agreed that prophylaxis for latent tuberculosis would be suspended for 1 year. A high-resolution CT scan of the chest was performed prior to vaccination and then 10 weeks after vaccination. Twelve initial participants entered the trial; 9 were recruited from TB contact clinics.

**Results:** The majority of patients demonstrated a local irritant effect after vaccination that included some redness, itching, pain, and induration. Most of the patients also had other symptoms, such as fever, flulike symptoms, arthralgia, headache, myalgia, nausea, fatigue, and 1 patient had syncope. There was a significant increase in the number of IFN-gamma-secreting T cells responding to the antigen from the vaccine within 1 week post-vaccination. This increase remained constant throughout the entire follow-up. The magnitude of this response was considerably higher than that which had been previously reported when patients were exposed to bacillus Calmette-Guérin vaccine. There was also a significant increase at 1 week in interleukin-2 (IL-2) producing T cells. The population of the CD4 T cell populations that were able to produce the cytokines IFN-gamma, IL-2, and tumor necrosis factor-alpha were also increased. There was no change in findings on CT scans after vaccination.

**Conclusions:** The authors conclude that MVA85A is safe and creates immunogenicity in individuals with latent TB. However, further trials appear to be in order.

**Reviewer's Comments:** This new vaccination appears to have more immunogenicity than the previous vaccination and does not appear to do any harm to patients with latent TB. Obviously, this was an extremely small study, and the likelihood of greater incidence of side effects and or other problems associated with the vaccine can only be determined after significant study in highly endemic populations. However, if this is successful, this vaccine may have amazing implications for TB. (Reviewer-Eric H. Gluck, MD, JD).
**Objective:** To determine whether a forced expiration volume in 6 seconds (FEV₆) might be a substitute for standard FEV₁/FVC maneuver to simplify spirometry.

**Design:** Meta-analysis involving a MEDLINE search of articles published between 1966 and 2008; other data sources of noted literature archives were also searched, and the authors were contacted for further study details if necessary.

**Methods:** No language restrictions were used in this study. The authors included all studies that had diagnostic accuracy of the FEV₁/FEV₆ for a way of structuring compared to FEV₁/FVC providing both sensitivity and specificity. Two reviewers independently judged the study eligibility. Data were then extracted independently.

**Results:** 17 publications met the criteria for evaluation. Six of these studies, however, were excluded because they did not have data available to generate a sufficient comparison between the 2 techniques. One was excluded because it represented repeated data from another study. Therefore, just over 31,000 participants from 11 studies were available for evaluation. Of these, 10,000 had airway obstruction and 21,000 had normal airways. The pooled summary data showed that FEV₁/FEV₆ was an acceptable surrogate for FEV₁/FVC, with a sensitivity of 0.89 and a specificity of 0.98. The authors demonstrated that there was no evidence of a threshold effect. The receiver operating curve for the surrogate marker of FEV₁/FEV₆ was quite favourable, with an area under the curve of >0.9. Publication bias was evaluated using a funnel plot, which demonstrated symmetry suggesting that bias did not exist.

**Conclusions:** The FEV₁/FEV₆ is a sensitive and specific test for the diagnosis of airway obstruction and it can serve as a valid alternative for that diagnosis. The FEV₁/FEV₆ is a sensitive and specific test for the diagnosis of airway obstruction, and it can serve as a valid alternative for FEV₁/FVC to quantitate that diagnosis.

**Reviewer's Comments:** This is very good news and this is a well done meta-analysis. A robust number of patients were included in this study, and, therefore, the data are quite valid. The authors performed a final analysis to determine if it might have been a publication bias, and there was none. This is good news for our patients, since it is much simpler for them to perform the FEV₁/FEV₆ number than a forced out of capacity maneuver. This will then open this test not only for patients in the clinic, but perhaps for patients in the hospital as well. (Reviewer-Eric H. Gluck, MD, JD).

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Keywords: Detecting Airway Obstruction

Print Tag: Refer to original journal article
Is Embolization a Tx Option for HHT?

**Diffuse Pulmonary Arteriovenous Malformations in Hereditary Hemorrhagic Telangiectasia: Long-Term Results of Embolization According to the Extent of Lung Involvement.**

Lacombe P, Lagrange C, et al:

*Chest* 2009; 135 (April): 1031-1037

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HHT patients are at risk for paradoxical embolization. Interventional embolization can improve the physiology of this disorder and prevent this complication.

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**Objective:** To evaluate the safety and efficacy of embolization in patients with diffuse pulmonary arteriovenous malformations (PAVMs).

**Design/Participants:** This was a retrospective analysis of a database of patients who were identified with hereditary hemorrhagic telangiectasia (HHT).

**Methods:** Standard demographic data, as well as laboratory evaluations, were performed on all of the patients. The patients were classified as to what specific type of HHT they had. Standard techniques for embolization were employed. Patients had the procedure done under conscious sedation. Prophylactic antibiotics were administered. Patients were followed-up after the procedure with a full clinical evaluation conducted within 6 months following the intervention.

**Results:** From February 1992 to June 2007, 39 patients were identified; their average age was 35 years (range, 9 to 83 years). Ninety percent of the patients presented with dyspnea; cyanosis was present in 17 patients and clubbing in 11. Hemoptysis was reported in 18% of the patients. The average PaO₂ prior to embolization was around 65. Approximately 44% of the patients actually admitted to some neurological complication prior to the embolization, and stroke, transient ischemic attack, and abscess of the brain were reported in 4%, 4%, and 9%, respectively. Early complications occurred following embolization in approximately 20 patients. Complications included failed catheterization, arterial wall damage, transient ischemic attack, sudden deafness, fever, pulmonary infarct, the development of pleural effusion, and in 1 case, a lung abscess. The mean follow-up duration was 43 months. Three patients died from cerebral hemorrhage, myocardial infarction, and cerebral abscess, respectively. Improvement was noted in the respiratory symptoms in approximately 80% of the patients. There was also a significant increase in the arterial oxygen level following the procedure. Based on CT scan, there was a 59% success rate in embolization of the pulmonary arteriovenous malformation.

**Conclusions:** The authors concluded that paradoxical embolization is a frequent complication in patients with involvement of every subsegmental artery of at least 1 lobe. Prevention of these complications and improvement in patient dyspnea can be achieved using embolization.

**Reviewer’s Comments:** This is actually a very nice mini review of a very uncommon disease, HHT. It also provides reasonable insight into potential treatment for this rare disorder, which appears to be embolization rather than surgical treatment. It would also appear that in at least approximately 60% of patients, significant improvement in quality of life and reduced risk for complications can be achieved through this procedure (Reviewer-Eric H. Gluck, MD, JD).

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Keywords: Rare Lung Diseases

Print Tag: Refer to original journal article
Small Volumes of Pleural Effusion Are Diagnostic of Malignant Effusions

A Prospective Study of the Volume of Pleural Fluid Required for Accurate Diagnosis of Malignant Pleural Effusion.

Abouzgheib W, Bartter T, et al:

Chest 2009; 135 (April): 991-1001

Fifty mL of pleural fluid has the same exact diagnostic yield as larger volumes.

Objective: To evaluate whether 50 mL of pleural fluid was sufficient when compared to a larger volume of fluid in making the diagnosis of malignant pleural effusion.

Participants/Methods: Patients were enrolled between 2003 and 2007; most of the enrolled patients were having a diagnostic thoracentesis for evaluation of potential malignancy. Standard technique was used for performing the procedure. The first 50 mL of the fluid was typically obtained using a syringe and placed in a specimen cup. The rest was placed in a large drainage bag. The first sample was centrifuged and supernatants were removed and the cell pellet was prepared for evaluation. The large volume of fluid collected in the collection bag was evaluated using standard techniques.

Results: 44 patients were included in the study (21 men and 23 women). The patients' average age was 46 years, and the mean volume of the large-volume specimen was approximately 890 mL. Thirteen patients had a prior history of cancer. Cytologic evaluation was positive for malignancy in 55% of the cases. In all cases, when a malignant pleural effusion was eventually diagnosed, both the specimen from the large volume and the mL initial specimen were positive. In patients with negative pleural effusion for malignancy, both specimens also demonstrated concordance. In patients with a prior history of cancer or an established history of cancer, the pleural effusion was positive for malignant cells in approximately 58% of the patients.

Conclusions: Submission of specimens of approximately 50 mL of pleural fluid for cytologic evaluation is adequate; larger volume specimens do not increase the likelihood of a positive diagnosis.

Reviewer's Comments: This is a pretty simple study that answers a specific question about the volume of fluid necessary to achieve a high likelihood of making a diagnosis of malignancy when one is present. The authors have demonstrated, albeit with relatively small numbers (only about 50 patients in the study), that only 50 mL of specimen are necessary. This might be important in some patients since if the results are positive and a pleurodesis is anticipated, having some fluid left in the chest makes the subsequent procedure a lot easier. Possibly, there might actually be a reduced number of complications when one only needs to remove a smaller volume of fluid from these patients. (Reviewer-Eric H. Gluck, MD, JD).

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Keywords: Malignant Pleural Effusion

Print Tag: Refer to original journal article
Objective: To review the incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE) following podiatric surgery.

Participants/Methods: The data came from a large not-for-profit Health Maintenance Organization database. Patients were identified from the medical electronic record if they had undergone a podiatric procedure. Both inpatient procedures and outpatient procedures were evaluated; patients were then evaluated to determine if they developed a post-procedure venous thromboembolic (VTE) event. Patients who did develop VTE reactions were then screened for the presence of cancer, a prior history, known hypercoaguable state, age, presence of obesity, and use of hormonal replacement therapy (HRT).

Results: More than 7200 patients underwent >16,040 podiatric procedures from December 1999 through November 2004. Of these 7200 patients, there were only 12 symptomatic DVTs and 10 symptomatic PE, for an incidence of <0.2% for both. There was no fatal PE. The mean time between surgery and VTE event was 52 days, but most of the cases occurred within the first 3 months. Three risk factors were identified that were significantly associated with post-procedure DVT or PE. These included prior history, obesity, and use of HRT. Patients with a prior history had a procedure-related incidence of 4.6%. For obese patients, the rate was 0.48%, and for patients on HRT or oral contraceptives, the incidence was 0.55%. A regression analysis demonstrated these to be independent risk factors. Other risk factors that are typically associated with VTE disease, including cancer, hypercoagulable state, and advanced age, were not associated with VTE disease and post-podiatric procedures.

Conclusions: There is a low overall risk for VTE disease in podiatric patients, suggesting that routine use of prophylaxis is not warranted. Those patients with a prior history of DVT, however, might benefit from the use of prophylactic heparin following surgery. The authors also suggested that patients with ≥2 risk factors might be considered for prophylaxis as well.

Reviewer's Comments: I am a bit surprised by the results of this study. I would have thought that the combination of a surgical procedure, which in some instances does involve surgery on the bone as well as the likelihood that there would be a reduction in mobility following surgery, might have increased the risk for VTE disease in these patients. Fortunately, these data demonstrate that that is not the case. (Reviewer-Eric H. Gluck, MD, JD).
Objective: To determine if tight or conservative glucose control has an impact on mortality in critically ill patients in the ICU.

Participants/Methods: Patients were enrolled in the study if they were receiving treatment in an ICU for at least ≥3 days. Enrollment occurred within the first 24 hours of admission and then the patients were randomized to either intensive glycemic control with a blood sugar goal of between 81 and 108 or conventional glycemic control with a blood sugar goal of ≤180. The primary end point for the study was death from any cause within 90 days of entrance to the study. Control of the blood sugar was achieved using IV infusion of insulin. Capillary samples were discouraged. A blood sugar ≤40 was considered a serious adverse event.

Results: 6104 patients were enrolled in the study; 3050 were assigned to the conventional treatment with the rest assigned to intensive glycemic control. At baseline, the demographic and clinical data between the 2 groups were fairly similar. Ninety days after randomization, 27.5% in the intensive-glycemic control group had died compared with 24.9% in the conventional-treatment group, which was a statistical difference. The median survival time was lower in the intensive-glycemic control group than in the conventional group, and death from cardiovascular disease was more common in the intensive-glycemic control group compared to the conventional group. There was no difference in median length of stay in the ICU or hospital, and there was no difference in additional end-organ damage between the groups once they were enrolled in the study. Severe hypoglycemia occurred in approximately 7% of patients receiving intensive control compared to only 0.5% of those receiving conventional control. No long-term sequelae of severe hypoglycemia were reported in either group.

Conclusions: Intensive glucose control increased mortality in adults in the ICU. Patients who had a target value of 180 resulted in a lower mortality than in patients who had a target value of 81 to 108.

Reviewer’s Comments: This is the second study to demonstrate that very tight glycemic control results in increased morbidity and mortality. However, in both studies, there was no direct link between episodes of hypoglycemia and mortality. Therefore, it is difficult to understand what the mechanism for mortality might be. It is possible that some metabolic derangements occur when the blood sugars are <80 that does not result in the neurological deficits, but does change intracellular mechanics. At the present time, it would appear that loosening of the glucose end points is probably in order, and based on these last 2 studies, should be directed to a level of between 150 and 180. (Reviewer-Eric H. Gluck, MD, JD).
Desmoteplase May Be Equivalent to Alteplase in Acute Massive PE

Desmoteplase in Acute Massive Pulmonary Thromboembolism.

Tebbe U, Bramlage P, et al:

Thromb Haemost 2009; 101 (March): 557-562

There is a relatively low rate of major bleeding in this trial comparing thrombolytics in massive PE.

**Background:** Alteplase is currently the standard thrombolytic of choice. A novel plasminogen activator (Desmoteplase), which has particularly high fibrin specificity, has been recently identified.

**Objective:** To evaluate the efficacy of desmoteplase in management of massive pulmonary embolism (PE).

**Design:** Open-label randomized trial.

**Participants:** Patients aged 18 to 80 years with clinical evidence of massive PE in the preceding 14 days were enrolled. A mean pulmonary artery pressure >25 mm Hg and a pulmonary vessel occlusion of >50% were required, with no increased risk of bleeding.

**Methods:** Patients received either (1) desmoteplase 125 μg/kg as a bolus over 1 to 2 minutes or (2) alteplase as a 10-mg bolus with 90 mg infused over 2 hours. In the second and third phases of the trial, alteplase was compared with desmoteplase escalated to 180 μg/kg and then 250 μg/kg. All patients received unfractionated heparin. Efficacy end points were total pulmonary resistance, mean pulmonary artery pressure, and percentage of vessels occluded.

**Results:** Of the 34 patients enrolled, 22 were randomized to alteplase: 7 at 125 μg/kg, 9 at 180 μg/kg, and 6 at 250 μg/kg. The majority of patients were randomized within 2 to 5 days of onset of PE symptoms. With the exception of desmoteplase at 125 μg/kg, all treatment groups had a comparable decrease of total pulmonary resistance (TPR) of approximately one-third. There was a statistically significant decrease in TPR by approximately 50% at 6 hours in the 250-μg/kg group; however, all groups were similar at 24 hours except for the desmoteplase 125-μg/kg group, which had less efficacy. The largest drop in mean pulmonary artery pressure was seen at 6 hours in the desmoteplase 250-μg/kg group, and this was maintained at 24 hours, although it did not reach statistical significance. No statistically significant difference was observed in percent pulmonary artery occlusion as measured by pulmonary angiography or in mortality. One patient in the 250-μg/kg group died 6 days after treatment due to recurrent thromboembolism. Five patients had serious adverse events related to treatments.

**Conclusions:** Desmoteplase at 180 and 250 μg/kg had similar efficacy to that of alteplase.

**Reviewer's Comments:** This small study showed non-inferiority between desmoteplase and alteplase for acute massive PE. There was a speedier reduction of TPR after desmoteplase, but the other hemodynamic data did not correlate with this finding, and it was not convincing that desmoteplase was better. Relatively few deaths occurred in this cohort, so mortality could not be compared; in addition, relatively few serious adverse events occurred and no cases of intracranial hemorrhage occurred in this cohort, but the study is too small to compare safety. If the drug pricing is favorable, it might be worth considering using this drug, but this study alone does not support a change. (Reviewer-Anna R. Hemnes, MD).

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Keywords: Acute Massive Pulmonary Thromboembolism

Print Tag: Refer to original journal article
Obesity Not Risk Factor for ARDS After Traumatic Injury

Obesity and Pulmonary Complications in Critically Injured Adults.
Dossett LA, Heffernan D, et al:
Chest 2008; 134 (November): 974-980

In this study, severely obese patients (BMI, ≥40) have a significantly decreased risk of developing ARDS after major trauma. This finding is consistent with a previously described “obesity paradox” in the ICU.

Background: While obesity is highly correlated with chronic illness, less is known about its influence on critical illness.
Objective: To determine the association of body mass index (BMI) and the risk of pulmonary complications (acute respiratory distress syndrome [ARDS], pneumonia, and tracheostomy) in patients admitted to trauma ICUs.
Design/Participants: Prospective, multicenter, cohort study of adult patients admitted to trauma ICUs at Vanderbilt University Medical Center and the University of Virginia Medical Center. To exclude the minimally and the catastrophically ill, patients were only screened if their ICU stay was >48 hours.
Methods: 2291 patients were screened; 883 were excluded due to lack of traumatic injury and 187 were excluded due to lack of BMI data. The remaining 1219 patients were characterized as underweight (BMI, <18.5), normal weight (BMI, 18.5 to 24.9), overweight (BMI, 25.0 to 29.9), obese (BMI, 30.0 to 39.9), or severely obese (BMI, ≥40.0). Patients were followed for the development of ARDS (diagnosis based on standard criteria), pneumonia (positive sputum culture, new infiltrate, and systemic evidence of infection), or tracheostomy. Secondary outcomes included in-hospital mortality and length of stay.
Results: The percentages of obese (23.0%) and severely obese (6.6%) patients in this cohort were comparable to national estimates. Obese and severely obese patients were less injured than normal patients as quantified by the trauma-related injury severity score (TRISS). In an unadjusted analysis of variance, the obese and severely obese had a longer length of ICU stay and a longer duration of mechanical ventilation. Surprisingly, the severely obese had a lower risk of ARDS than other weight groups. Even after controlling for age, gender, TRISS, and head Abbreviated Injury Score (a measure of injury severity), the severely obese had a lower risk of ARDS (OR, 0.36) compared to normal weight patients (95% CI, 0.13 to 0.99). BMI class was not associated with pneumonia, tracheostomy, or death.
Conclusions: After controlling for severity of trauma, age, and gender, severely obese trauma ICU patients had a 64% decreased risk of developing ARDS than did their normal weight counterparts. While obesity increased length of stay and ventilator time, it did not influence the risk of pneumonia, tracheostomy, or death.
Reviewer’s Comments: The authors’ findings of a potential protective effect of obesity are counterintuitive. Surprisingly, this observation is not an unusual one: many reports link obesity to improved ICU survival from a variety of insults, including ARDS. What this “obesity paradox” represents is the subject of vigorous debate. Do subtle alterations exist in how practitioners care for the severely obese (an increased likelihood of deep vein thrombosis prophylaxis, for example)? Is adipose tissue associated with a protective hormonal milieu of “adipokines?” Is the heavy ICU patient simply one who has been vigorously fluid-resuscitated? The answers to these questions promise improvement in ICU care for patients of all weights. (Reviewer-Eric P. Schmidt, MD).

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Keywords: Obesity

Print Tag: Refer to original journal article
ARDS Is Associated With Depression and Cognitive Dysfunction

Self-Reported Symptoms of Depression and Memory Dysfunction in Survivors of ARDS.

Adhikari NKJ, McAndrews MP, et al:

Chest 2009; 135 (March): 678-687

Patients with ARDS (even when they recover) have some comorbidities, such as depression, PTSD, and cognitive dysfunction, which may be life altering.

**Background:** Acute respiratory distress syndrome (ARDS) is an inflammatory syndrome of multiple etiologies. We already know that many patients develop post-traumatic stress disorder (PTSD) as a result of this. Typically patients are ventilated and sedated during a significant portion of the ICU stay.

**Objective:** To determine the prevalence of cognitive dysfunction and depression in patients who survive ARDS.

**Participants/Methods:** Patients were administered the Beck Depression Inventory-II scale and a memory dysfunction evaluation after discharge from the hospital after having an episode of ARDS. These patients had been previously enrolled in another ARDS study. Standard criteria were used for the presence of ARDS. Patients were evaluated at least 6 months and up to 48 months post-discharge; the median time was 22 months. The completion rate for the evaluations was approximately 75%.

**Results:** The average age of the participants was 42 years. Approximately 54% of the subjects had minimal depression based on the Beck scale, while 18% had severe depression. Patients with severe depression were less likely to be able to return to work. Eight percent of patients had significant memory deficit, and almost 20% had some memory deficits. There were no data collected during the illness that appeared to be predictive of these outcomes. Data did not change when the analysis was limited to patients who were English speaking.

**Conclusions:** Patients who have ARDS frequently have their condition complicated by depression and memory dysfunction that can be detected as early as 6 months post-illness and can last as long as 48 months or more. Depression was a factor in allowing the patients to once again lead a productive life and return to work.

**Reviewer’s Comments:** This is a very interesting study that demonstrates that patients with ARDS (even when they recover) have some comorbidities that may be life altering. It has already been demonstrated that many patients with ARDS develop PTSD and that this can have a significant negative impact on their life. Now we can see that depression and cognitive dysfunction are fairly prevalent as well. Unfortunately, the authors do not shed any light on the mechanism. Is this a direct effect of the inflammation on the brain or is this a side effect of sedation, mechanical ventilation, or some of the other medications that are used? Since there are a significant number of ARDS cases, this could present an important economic impact. (Reviewer-Eric H. Gluck, MD, JD).

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Keywords: Comorbidities

Print Tag: Refer to original journal article
Patients hospitalized for exacerbations of COPD have a significant risk of PE.

**Background:** In approximately 30% of cases, the cause of an exacerbation of chronic obstructive pulmonary disease (COPD) cannot be determined. Studies have shown that there is a 2-fold increase in risk for pulmonary embolism (PE) in patients with COPD.

**Objective:** To determine if there is a high prevalence of PE in patients with acute exacerbations of PE.

**Methods:** A comprehensive literature search was performed from 1982 to 2008 and included articles that had prevalence rates of PE during acute exacerbations of COPD or had CT or other diagnostic studies for PE within 48 hours of patients’ admission. Studies were excluded if they were retrospective or if PE was diagnosed solely by ventilation/perfusion (V/Q) scan or by autopsy.

**Results:** Data extracted from the articles included demographics, symptoms and signs, medication history, and severity of COPD. Over 2400 articles were identified, but only 5 met the rigid criteria set forth by the authors. These 5 articles included data for 550 patients with a 19.9% prevalence of PE among the group. Interestingly, the prevalence of deep vein thrombosis (DVT) was lower than that of PE. Risk factors for PE included a prior history of DVT, malignancy, and a recent history of surgery. In 1 study, patients with PE were more likely to complain of chest pain and syncope, while they were less likely to have a cough or purulent sputum. However, in general, the symptoms for patients with and without PE were about the same. Similarly, chest x-ray and electrocardiogram did not distinguish between patients with and without PE.

**Conclusions:** Patients who are hospitalized for acute exacerbations of COPD have a significant risk of PE, and careful assessment of these patients is important.

**Reviewer's Comments:** I fear that this article will provoke the almost routine use of CT in patients who are admitted for acute exacerbations of COPD. In fact, PE studies done in most hospitals are only positive approximately 15% of the time. Here the prevalence of the disease is higher than that. The authors did not identify how large the emboli were, and we do not know how acute they were either. Of note is the fact that DVT prevalence was lower, begging the question of where do the emboli come from or are they forming in situ? (Reviewer-Eric H. Gluck, MD, JD).

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Keywords: Pulmonary Embolism

Print Tag: Refer to original journal article
Using the neural signal from the diaphragm can reduce the work load of the respiratory muscles and reduces respiratory drive.

**Background:** It is possible to use signals from the diaphragm, which represent respiratory drive to deliver an appropriate flow rate and volume to meet the patient's demands. The net result is respiratory muscle unloading in proportion to the level of assist, which can be used as a primary mode of ventilation and seamlessly allow for weaning as well.

**Objective:** The authors examined the extent to which neurally adjusted ventilatory assist (NAVA) can unload respiratory muscle and whether it is sustainable when implementing a NAVA level that is adequate (NAVAal) during a titration procedure.

**Participants/Methods:** Patients were enrolled in the study if they were adults, in the ICU and requiring ventilatory support, and had oxygenation requirements of acute lung injury. The assist mode was controlled by diaphragmatic electrical activity. The delivered tidal volume was determined by multiplying the electrical signal by a proportionality factor. This signal also served as the trigger and cycling signal. The signal was first titrated to remove all respiratory drive and then decreased.

**Results:** The pressure time product measured via the esophagus was reduced by 74% using the neural signal at the maximal signal. Tidal volumes averaged about 6 mL/kg with ventilatory rates of 29 breaths per minute. The mean inspiratory pressure averaged 16 cm water. There were no significant changes noted in the hemodynamics or the oxygenation parameters that were measured. When compared to the settings while the patient was on conventional ventilation, the tidal volume was lower, the respiratory rate higher, and the airway pressure was lower using the neural signal.

**Conclusions:** The authors conclude that using the neural signal from the diaphragm can reduce the work load of the respiratory muscles and reduce respiratory drive.

**Reviewer's Comments:** For decades, we have been searching for a better trigger than the change in airway pressure. It has been long felt that a neural signal would be the best since this is the signal generated by the brain stem after assessing all the necessary inputs to result in optimal ventilation. This study demonstrates that it is possible to use an electrical signal from the diaphragm to allow for better titration of the ventilatory parameters to unload the respiratory muscles. (Reviewer-Eric H. Gluck, MD, JD).

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Keywords: Neurally Adjusted Ventilatory Assist

Print Tag: Refer to original journal article
Objective measures of cough profile, including expulsive phase rise, volume acceleration, and peak flow, have much better correlations with ROC areas of >0.86 for all 3.

**Background:** Aspiration of gastrointestinal contents is a concern for almost every patient in the ICU. Of particular concern are patients with neurologic disease, where certain reflexes might be diminished increasing the risk for aspiration and reducing the ability of the patient to respond to the vomiting.

**Objective:** Since the main protective process of the airway is the cough reflex, the authors of this paper decided to try to objectively measure cough and see if it was predictive of aspiration.

**Participants/Methods:** Stroke patients were identified and categorized by site and size of infarct. A speech pathologist performed a swallow evaluation. A neurocognitive test was also administered. Cough was assessed with respect to duration, volume, and acceleration. Measurements of aerodynamics and sound pressure were obtained using the PERCI-SAR system, which employs a tight fitting mask over the oral nasal area. Velocities of the air movement and the sound amplitude were recorded.

**Results:** Based on the swallow evaluation, 34% of the patients were felt to be high risk for aspiration. Clinical signs, such as inability to initiate swallowing, difficulty handling secretions, or cough immediately after drinking, had a sensitivity of 58% and a specificity of 83% for detecting aspiration. Objective measures of cough profile, including expulsive phase rise, volume acceleration, and peak flow, had much better correlations with ROC areas of >0.86 for all 3.

**Conclusions:** The measure of voluntary cough can predict patients who are at risk for aspiration and can be an adjunct to the basic clinical evaluation.

**Reviewer's Comments:** The first study that I saw regarding objective evidence of adequacy of cough was many years ago, but dealt with the measurement of cough velocity. Here too, parameters that deal with the effectiveness of the cough appear to be better than just a clinical evaluation. Unfortunately, what was not identified here was whether any of the aspirations that were identified were actually clinically relevant. It is estimated that <10% of all aspirations result in actual lung disease. We may be making much ado about nothing. (Reviewer-Eric H. Gluck, MD, JD).

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Keywords: Cough/Aspiration

Print Tag: Refer to original journal article
Three of the genetic markers previously identified in patients with COPD are also identified as being associated with hypoxia and PAP elevation.

Background: Chronic obstructive pulmonary disease (COPD) is not expressed equally in all individuals who smoke. Therefore, one would have to surmise that there are other factors that play a role in defining how significant COPD will be for a given amount of cigarette consumption. Data have been discovered that have identified environmental risk factors, such as pollution exposure.

Objective: To evaluate the prevalence of certain genes in patients who have COPD and try to determine if there is an increased risk associated with them.

Participants/Methods: Patients were obtained from an ongoing genetic study (the National Emphysema Treatment Trial [NETT]). Five genes already identified in patients with COPD were evaluated. Statistical methods were used to correlate $PO_2$, $PCO_2$ and pulmonary artery pressure (PAP) with the presence of 1 or more of these genetic mutations.

Results: 389 subjects were enrolled and studied. Two of the genetic defects were associated with hypoxia. Only 1 was associated with an elevation of the PAP. This was a different mutation than that which was associated with hypoxia. The authors then evaluated the genetic defect in patients who had COPD and were using home $O_2$ from a different cohort. They also found that the 2 identified genetic defects were present in this cohort with a prevalence that could not be anticipated by chance alone.

Conclusions: 3 of the genetic markers previously identified in patients with COPD were also identified as being associated with hypoxia and PAP elevation.

Reviewer's Comments: This is a very interesting study. It begins to shed light on the tremendous variation of disease in patients who smoke similar amounts. Since these are single site mutations, they are unlikely to be caused by the smoking. These mutations however, appear to make the likelihood of hypoxia or PAP elevation more likely. Further study is obviously in order. In the future, we might be screening all smokers for the presence of these markers. (Reviewer-Eric H. Gluck, MD, JD).

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Keywords: Genetics

Print Tag: Refer to original journal article
Background: With the increasing use of inhaled corticosteroids in both asthma and chronic obstructive pulmonary disease (COPD), more attention has been turned to the potential adverse effects of these medications. It has been widely known and accepted that only a small portion of these medications are absorbed systemically, but they can result in adrenal axis inhibition and osteoporosis.

Objective: To determine whether there might be an effect on serum glucose.

Participants/Methods: The patients for this study were enrolled from outpatient clinics from 7 different Veterans Administration (VA) medical centers. All patients had the diagnosis of COPD, and all had used inhaled steroids. Patients were required to have at least 80% adherence and at least 1 glucose measurement. All dosages were indexed to an equivalent dose of triamcinolone. Standard demographic data were collected from the VA electronic health care records.

Results: Almost 1700 patients were screened and enrolled in the study. Data were obtained from the VA database for both diagnosis and for the use of the medication. Compliance with the medication was calculated from the need for refills of prescriptions. The average daily dose of inhaled steroids was 621 μg. Nineteen percent of the patients had a self-reported history of diabetes mellitus. After controlling for systemic steroid use, as well as other potential confounding influences, there was NO association in nondiabetics of inhaled corticosteroid use and serum glucose measurements. There was, however, a dose response relationship seen in diabetics with the use of inhaled corticosteroids. For every increase in dosage of 100 μg, there was an increase in serum glucose of almost 2 mg/dL. Interestingly, patients who were receiving antihyperglycemic medications had a greater increase in blood sugar than diabetics who were not on these medications and controls.

Conclusions: The authors conclude that the use of inhaled corticosteroids is associated with elevations of blood sugars in diabetics in a dose response manner, but not in normal subjects.

Reviewer's Comments: This study resolves a relatively important question. Glucose levels appear to be adversely affected by inhaled corticosteroids, but only in diabetics, especially those on oral hypoglycemic medications. Therefore, when initiating this form of therapy in elderly patients with both COPD and diabetes mellitus, vigilant monitoring of glucose levels is in order. (Reviewer-Eric H. Gluck, MD, JD).

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Keywords: Inhaled Corticosteroid Use

Print Tag: Refer to original journal article
DES as Safe as Bare-Metal Stents

Long-Term Safety and Efficacy of Drug-Eluting Versus Bare-Metal Stents in Sweden.

James SK, Stenestrand U, et al:


The long-term outcomes for bare-metal stents and DES are similar, but the DES provides significant protection against early restenosis.

Background: Recently there has been a lot of attention drawn to the safety of drug-eluting stents (DES). A large study had shown increased mortality associated with their use. However, we reported a follow-up study that suggested that they were safe and efficacious.

Objective: These next data are from a similar study from Sweden.

Participants/Methods: Almost 48,000 patients were evaluated between 2003 and 2006 if they underwent a procedure resulting in stenting of a coronary artery. Follow-up data up to 5 years post-procedure were available. The evaluation compared the outcomes for all the patients who had only 1 stent placed. The mean duration of follow-up was approximately 3 years.

Results: In the group as a whole, there were 2380 deaths and 3198 myocardial infarctions (MIs). There was NO difference between the 2 groups for the combined end point of death or MI. The relative risk for these events in the DES patients was 0.96. When separated, there was also no difference between the 2 treatment groups for either death or MI. There was 1 adherence seen in that patients who received DES in 2003 had a slightly higher incidence of late events, but this was not true for patients who received the same stents in later years. There was a lower rate of re-occlusion in the patients who received the DES compared to the bare-metal stents at 3 events per 100 patient-years compared to 4.7 events in the bare-metal group. This was statistically different. The number needed to treat with DES to save 1 restenosis was calculated to be 39. Patients who were stratified as high risk actually had a more profound improvement with the DES when compared to the bare-metal stents. In this group, the number needed to treat was only 10.

Conclusions: The long-term outcomes for bare-metal stents and DES were similar, but the DES provided significant protection against early restenosis.

Reviewer’s Comments: I think that this study, especially when combined with other registry studies and a meta-analysis, now clearly establishes the safety of DES in patients with acute coronary syndrome. There appears to be a benefit for the patient against restenosis, although both stents appear to have a similar long-term outcome benefit. (Reviewer-Eric H. Gluck, MD, JD).

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Keywords: Stents

Print Tag: Refer to original journal article