EVIDENCE-BASED INFORMATION FOR HOSPITALISTS, INTENSIVISTS, AND ACUTE CARE CLINICIANS

HOSPITAL MEDICINE ALERT

AHC Media LLC Home Page—www.ahcpub.com

CME for Physicians—www.cmeweb.com

AHC Media LLC

INSIDE

Financial Disclosure

Hospital Medicine Alert's physician editor, Kenneth P. Steinberg, MD, has no relevant financial relationship related to the material presented in this issue.

Are Routine Daily Chest X-Rays Justifiable in the ICU?

ABSTRACT & COMMENTARY

By David J. Pierson, MD

Professor, Pulmonary and Critical Care Medicine, Harborview Medical Center, University of Washington

Dr. Pierson reports no financial relationships relevant to this field of study.

This article originally appeared in the April 2007 issue of Critical Care Alert. It was peer reviewed by William Thompson, MD. Dr. Thompson is Staff Pulmonologist, VA Medical Center; Associate Professor of Medicine, University of Washington. Dr. Thompson reports no financial relationships relevant to this field of study.

Synopsis: *Elimination of daily routine CXRs reduced the number of CXRs in a mixed medical-surgical ICU, while not affecting readmission rate and ICU and hospital mortality rates.*

Source: Graat ME, et al. Elimination of daily routine chest radiographs in a mixed medical-surgical intensive care unit. *Intensive Care Med.* 2007:33:639-644.

Graat and colleagues at the University of Amsterdam in The Netherlands, conducted this prospective study to determine the impact of discontinuing daily chest radiographs in the ICU. The ICU in question is a closed, 28-bed unit, admitting medical, cardiac, surgical, and trauma patients in a tertiary care hospital. For 5 months in 2004, while a policy of routine daily chest X-rays was in effect, the investigators tracked all chest X-rays obtained on patients in the unit, both routine and for specific indications. After a one-month interval, during which policy changed and obtaining routine daily chest X-rays was discontinued, Graat et al tracked all films obtained during a second 5-month period. During the latter interval, chest X-rays were obtained on ICU admission, following insertion of central lines or intravascular devices, following intubation, after insertion of chest tubes, with an increase in oxygen requirements, or with a change in pulmonary secretions suggestive of pneumonia.

A total of 5161 chest X-rays were obtained during the study — 3894 films on 754 patients while the policy of daily X-rays was in effect, and 1267 films on 622 patients after it was dis-

Hospital Medicine Alert's physician editor, Kenneth P. Steinberg, MD, selected and reviewed the articles contained within this issue on April 10, 2007.

continued. The patients in the second phase were older (62 vs 60 years), and fewer of them underwent cardiac surgery (both, $P < 0.05$). Otherwise, the patients managed in the ICU during the 2 intervals were similar. Using predefined criteria for unexpected radiographic abnormalities, there were 147 such findings during the first interval — in 10.2% of on-demand chest X-rays — of which 57 (3.9%) led to a change in therapy. In the second interval, after daily chest X-rays were stopped, there were 156 unexpected abnormalities — in 1.6% of on-demand chest X-rays — of which 61 (4.8%) led to a change in therapy. The slight increase in unexpected abnormalities on non-routine films, and the frequency with which these were associated with a change in therapy, were both statistically significant ($P < 0.05$). ICU length of stay, readmission rate, and mortality in the ICU and in the hospital did not differ in the 2-study intervals.

COMMENTARY

Studies have shown that patients in ICUs, particularly intubated patients on mechanical ventilation, have a high incidence of radiographic abnormalities. Because other bedside tools, such as history and physical examination are imperfect in the high-stakes task of detecting changes in critically ill patients, the daily morning chest X-ray has long been assumed to be an important management component. However, this is only the most recent in a series of studies whose findings cast doubt on that assumption.

The present study is an extension of one published a year ago by the same group of investigators.[1] In that earlier study, Graat et al sought to determine how frequently unexpected, predefined abnormalities were identified on routine daily chest X-rays in their unit, and how often such changes resulted in changes in management. They evaluated 2457 daily films obtained in 754 consecutive patients over a 5-month period. In 14.3% of these patients (5.8% of daily chest X-rays), an unexpected abnormality found. The latter included large atelectasis (24 instances), large infiltrates (23 instances), severe pulmonary congestion (29 instances), large pleural effusions (13 cases), barotraumas (pneumothorax or pneumomediastinum, 14 cases), and malposition of the endotracheal tube (32 instances). Graat et al judged that in only 2.2% of all daily routine chest X-rays was an abnormality found that resulted in a change in management. These findings did not differ in medical vs surgical patients.

There are several potential criticisms of the present study. For one thing, the first observation period was March through July, and the second was September through January, with significant differences in patient age and admitting diagnoses between those groups. How these differences might have affected the incidence of complications and their radiographic manifestations is unclear, but examining the same time period during 2 different years would have been a cleaner design. More importantly, perhaps, it is uncertain whether length of stay, readmissions, and ICU and hospital mortality are the only relevant outcomes to which the question of daily chest X-rays might pertain.

Still, it is probably appropriate to question whether simply being in an ICU warrants a daily chest X-ray. In the absence of clinical suspicion that something might have changed, this is probably something that can be safely omitted in most circumstances, particularly for patients who are not intubated or at increased risk for respiratory complications ■

Reference

1. Graat ME, et al. The clinical value of daily routine chest radiographs in a mixed medical-surgical intensive care unit is low. *Crit Care.* 2006;10:R11.

Hospital Medicine Alert, ISSN 1931-9037, is published monthly by AHC Media LLC, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

SENIOR VICE PRESIDENT/GROUP PUBLISHER: Brenda Mooney.
ASSOCIATE PUBLISHER/EDITORIAL GROUP HEAD: Lee Landenberger.
MANAGING EDITOR: Leslie Hamlin.
MARKETING PRODUCT MANAGER: Shawn DeMario.

GST Registration Number: R128870672.
Periodicals postage paid at Atlanta, GA.
POSTMASTER: Send address changes to ***Hospital Medicine Alert***, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $42. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

Subscriber Information

Customer Service: 1-800-688-2421
Customer Service E-Mail: customerservice@ahcmedia.com
Editorial E-Mail: leslie.hamlin@ahcmedia.com

Subscription Prices

United States
1 year with Free *AMA PRA Category 1 Credits™*: $249
Add $9.95 for shipping & handling.
(Student/Resident rate: $125).

Multiple Copies
Discounts are available for group subscriptions. For pricing information, please call Tria Kreutzer at (404) 262-5482.

Canada
Add GST and $30 shipping.

Elsewhere
Add $30 shipping.

Accreditation

AHC Media LLC is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media LLC designates this educational activity for a maximum of *20 AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

This CME activity is intended for hospitalists, intensivists and acute care clinicians. It is in effect for 36 months from the date of the publication.

AHC Media LLC

Questions & Comments

Please call Leslie Hamlin, Managing Editor, at (404) 262-5416 or e-mail at leslie.hamlin@ahcmedia.com between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

Antithrombotic Prophylaxis for Patients with CVDs

ABSTRACT & COMMENTARY

By William B. Ershler

INOVA Fairfax Hospital Cancer Center, Fairfax, VA; Director, Institute for Advanced Studies in Aging, Washington, DC

Dr. Ershler is on the speaker's bureau for Wyeth, and does research for Ortho Biotech. This article originally appeared in the April 2007 issue of Clinical Oncology Alert. It was peer reviewed by VR Veerapalli, MD. Dr. Veerapalli is Staff Clinician, INOVA Fairfax Cancer Center. Dr. Veerapalli reports no financial relationships relevant to this field of study.

Synopsis: *Current AP schedules do not appear to prevent catheter-related thrombosis. Systemic VTE and mortality, however, appeared lower after prophylaxis.*

Source: Fagnani D, et al. Thrombosis-related complications and mortality in cancer patients with central venous devices: An observational study on the effect of antithrombotic prophylaxis. *Ann Oncol.* 2007;18:551-555.

THERE HAVE BEEN CONFLICTING STUDIES REGARDing the advisability of antithrombotic prophylaxis (with low-molecular weight heparin [LMWH], unfractionated heparin, or low-dose warfarin) in patients with cancer for whom indwelling central venous catheters have been employed.[1-5] Fagnani and colleagues from the POLONORD Group in northern Italy, report their observational prospective study designed to assess the management of central venous devices (CVDs) in patients treated in community practice, particularly in the context of antithrombotic prophylaxis (AP). Cancer patients from 18 hospital oncology units throughout northern Italy, were enrolled over a 30-month period (through June 2005) if they had a totally implantable CVD (port), an indwelling central venous catheter (CVC), or a peripherally-inserted catheter (PICC). The type of catheter used was at the discretion of the physicians at each hospital, as was the decision of whether or not to prescribe antithrombotic prophylaxis.

Data analyzed included demographic details, type of CVD, position of the catheter tip, type and stage of tumor, history with regard to prior thrombotic events, and past and current cancer treatments (chemotherapy, radiotherapy, hormone therapy and growth factors). One feature that separates this survey from others is the length of follow up. Evaluations on each patient were scheduled every 4 months during the first year, every 6 months during the second and third years, or until removal of the CVD. During follow up, a record was kept of any catheter-related complications (eg, infection, pneumothorax, catheter fracture, etc.), systemic thromboembolic events (eg, pulmonary embolism, DVT other than in the vicinity of the CVD, supraventricular tachycardia, etc.), CVD removal, bleeding episodes (eg, intracranial or retroperitoneal hemorrhage), and the course of the neoplastic disease (progression of disease, death). Furthermore, the type of antithrombotic prophylaxis was recorded as either associated with the procedure (limited to 48 hours at the time of catheter insertion) or continuous, and the type of anti-thrombotic therapy documented. The drugs employed, mini-dose warfarin per the Levine regimen[6] (initially 1 mg/day, tapered to maintain INR of 1.3-1.9), LMWH, or unfractionated heparin and duration of treatment were also recorded.

During the 2.5 years of study, 1410 consecutive patients were enrolled and 1390 were seen at least once in the 6- month median follow-up. There was no difference in catheter-related thrombosis in patients given antithrombotic prophylaxis or not (2.8% and 2.2%), and no major bleeding events were recorded. However, systemic (ie, not in the vicinity of the catheter) venous thrombus embolic events, including superficial thromboses and pulmonary embolism, were less frequent with antithrombotic prophylaxis (4% vs 8.2%, P = 0.005), and mortality was lower (25% vs 44%, P = 0.0001). Upon multilogistic regression analysis, only advanced cancer and no antithrombotic prophylaxis were significantly associated with mortality.

COMMENTARY

This is a very curious finding. Although antithrombotic prophylaxis did not prevent catheter-related thrombosis, it did seem to influence systemic thromboses, including the occurrence of pulmonary emboli and reduction of overall mortality. It's difficult not to be a little bit energized by this finding, albeit derived from an observational, nonrandomized study. Reluctantly, we must accept that AP is ineffective at reducing catheter-associated thrombus formation, as the current results confirm what several other studies have indicated previously.[2,5] Despite the theoretical appeal of such an approach, there is no evidence that anticoagulation prevents catheter-associated thrombus in cancer patients.

The lack of effect in the current study may be the

result of the relatively low incidence of catheter-associated thrombus in either group, those receiving prophylaxis (2.8%) and those not (2.2%). This, in turn, may reflect improved technique, catheter positioning, and the use of less thrombogenic devices. Furthermore, because this was a pattern-of-care type study, participating physicians may have chosen to use antithrombotic prophylaxis for those patients considered at highest risk (advanced disease, history of prior DVT, etc) and, accordingly, the 2.8% incidence might be lower than what would have been observed had this group not been treated.

That antithrombotic prophylaxis influenced non-catheter-associated thrombotic occurrence is remarkable and needs further explanation. The majority of patients who received prophylaxis were given low-dose warfarin, and there have been previous conflicting reports on the value of such treatment in preventing venous thrombosis in cancer patients.[6,7] The current study was large, well designed, and of sufficient duration to merit attention. The data would suggest that antithrombotic prophylaxis for patients with advanced cancer with a high risk for venous thrombosis achieve more favorable outcomes (less thromboembolic events and longer overall survival). However, because of the inherent risks associated with anticoagulation, a randomized, prospective study in carefully selected patients is called for. ■

References

1. Bern MM, et al. Very low doses of warfarin can prevent thrombosis in central venous catheters. A randomized prospective trial. *Ann Intern Med.* 1990;112: 423-428.
2. Couban S, et al. Randomized placebo-controlled study of low-dose warfarin for the prevention of central venous catheter-associated thrombosis in patients with cancer. *J Clin Oncol.* 2005;23:4063-4069.
3. Karthaus M, et al. Dalteparin for prevention of catheter-related complications in cancer patients with central venous catheters: Final results of a double-blind, placebo-controlled phase III trial. *Ann Oncol.* 2006;17:289-296.
4. Monreal M, et al. Upper extremity deep venous thrombosis in cancer patients with venous access devices — prophylaxis with a low molecular weight heparin (Fragmin). *Thromb Haemost.* 1996;75: 251-253.
5. Verso M, et al. Enoxaparin for the prevention of venous thromboembolism associated with central vein catheter: A double-blind, placebo-controlled, randomized study in cancer patients. *J Clin Oncol.* 2005;23: 4057-4062.
6. Levine M, et al. Double-blind randomised trial of a very-low-dose warfarin for prevention of thromboembolism in stage IV breast cancer. *Lancet.* 1994;343: 886-889.
7. Cortelezzi A, et al. Incidence of thrombotic complications in patients with haematological malignancies with central venous catheters: A prospective multicentre study. *Br J Haematol.* 2005;129:811-817.

Patent Foramen Ovale and the Risk of Stroke

ABSTRACT & COMMENTARY

By Jonathan Abrams, MD

Professor of Medicine, Division of Cardiology, University of New Mexico, Albuquerque

Dr. Abrams serves on the speaker's bureau for Merck, Pfizer, and Parke-Davis. This article originally appeared in the April 2007 issue of Clinical Cardiology Alert. It was edited by Michael Crawford, MD, and peer reviewed by Rakesh Mishra, MD. Dr. Crawford is Professor of Medicine, Chief of Clinical Cardiology, University of California, San Francisco, and Dr. Mishra is Assistant Professor of Medicine, Weill Medical College, Cornell University; Assistant Attending Physician, NewYork-Presbyterian Hospital. Dr. Crawford is on the speaker's bureau for Pfizer, and Dr. Mishra reports no financial relationships relevant to this field of study.

Synopsis: *Compared with a lower dose, intensive treatment with atorvastatin in patients with stable coronary disease significantly reduces hospitalizations for HF.*

Source: Di Tullio MR, et al. Patent foramen ovale and the risk of ischemic stroke in a multiethnic population. *J Am Coll Cardiol*. 2007;49:797-802.

A LONG-STANDING CONTROVERSY EXISTS REGARDing the importance of a patent foramen ovale (PFO) as a cause for TIA or stroke. This report is from NOMAS (Northern Manhattan Study), an epidemiologic study evaluating risk factors for, and the incidence of stroke in Northern Manhattan, New York City. The eligible study population had no history of a cerebral event. A total of 1100 subjects were recruited between 1993 and 1999. All had echocardiographic evaluation, a review of medical records, a physical/neurological exam, and standard blood work. Echo exams included agitated saline contrast, the

Valsalva maneuver, and coughing, all employed to increase sensitivity for detection of a PFO.

A PFO was confirmed by microbubbles seen in the left heart within 3 cardiac cycles, following maximum right atrial opacification. An atrial septal aneurysm (ASA) was sought, diagnosed by more than 10 mm of septal protrusion behind the plane of the septum to the left or right. Telephone follow-up was done with little loss of study participants. Any possible neurologic, cardiac, or vascular event triggered an in-person interview and assessment. Subjects suspected to have a possible stroke were seen by a neurologist. Stroke was defined by the TOAST Criteria. Ischemic stroke was verified by 2 independent neurologists.

The primary study outcome was the occurrence of fatal or nonfatal ischemic stroke. Kaplan-Meier and COX proportional hazards survival models were utilized. Adjustments were made for other stroke risk factors, including hypertension, diabetes, elevated lipids, smoking, and atrial fibrillation. The cohort of 1100 patients included more women than men (640 vs 460), with a median age of 69. African Americans comprised 26%, Hispanics 50%, and Caucasians 25% of the population.

Results: PFO was detected in 15% of the subjects, and ASA in 2.5%; both a PFO and ASA were noted in 1.7%, or 19. Groups with and without an event were similar. Aspirin utilization was not different between the 2 groups. Overall follow-up was 80 ± 28 months. Ischemic stroke occurred in 6.2% of the subjects, with a stroke incidence of 12.2 per 1000 person years, compared to PFO-positive individuals, 8.9 per 1000 person years (P = 0.5). After adjusting for all stroke risk factors, the hazard ratio of a PFO for stroke was nonsignificant, 1.64 (95%; CI, 0.87 to 3.09). Frequency of embolic, as well as cryptogenic stroke was not different in patients with or without PFO. An isolated ASA was unrelated, although the numbers were small. The non-association between PFO and ischemic stroke was not influenced by gender, age, or ethnicity. Di Tullio and colleagues conclude "the study shows no significant increase in the risk of ischemic stroke from PFO in the general population during a mean follow up of 7 years."

COMMENTARY

Because of the concern that PFO increases stroke risk, there have been a number of trials evaluating PFO closure devices. The potential world-wide market for such devices is very large. Many believe that a significant number of strokes in the United States are cryptogenic and could be caused by a thromboembolic event related to a PFO. The prevalence of a PFO in patients who have had a stroke is somewhat higher than that of strokes of known cause. Heretofore, there have been an inadequate number of truly randomized trials, and outcomes are uncertain. Many non-randomized trials have been published, usually favorable for PFO closure devices.

The present study, as well as other data raise the issue as to whether the question of PFO and cryptogenic stroke has been resolved. A recent commentary in *JAMA* discusses in detail the scope of the problem, as well as focuses on the regulatory background for device approval, with particular focus in the PFO closure devices of which 2 have been widely used in the United States (Maisel WH, Laskey WK. *JAMA*. 2005;294:366-368.). Maisel and Laskey emphasize the many unresolved questions in regards to efficacy, device complications, the lack of randomized trials, and other aspects of this controversy. They state, "PFO closure device approval for a more widespread indication mandates a more rigorous, evidence-based evaluation." They point out that the American Academy of Neurology practice guidelines conclude that there is insufficient evidence to recommend routine device closure of PFO in individuals with cryptogenic strokes.

The Stroke Counsel of the American Heart Association ". . .has called for physicians to enroll their patients in randomized clinical trials." While the present study does not support the association between PFO and cerebral embolic event, the adjusted and unadjusted data all trend toward such a relationship, but do not come close to statistical significance. New data, and the perceptive analysis of the state of the art, as well as previous studies published, indicate that there is no final answer regarding efficacy and safety of routine PFO closure. Physicians need to carefully consider the therapeutic options available following the identification of a PFO in an individual who has not suffered a cerebral event, or in a population of patients who have had a cryptogenic stroke. Finally, the question remains related to devices: Is the horse already out of the barn? ■

Statins for Heart Failure?

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

This article originally appeared in the April 2007 of Clinical Cardiology Alert. It was edited by Rakesh Mishra, MD.

Synopsis: *Compared with a lower dose, intensive treatment with atorvastatin in patients with stable coronary disease significantly reduces hospitalizations for HF.*

Source: Khush KK, et al. Effect of high-dose atorvastatin on hospitalizations for heart failure: Subgroup analysis of the Treating to New Targets (TNT) study. *Circulation*. 2007; 115:576-583.

THE ROLE OF STATINS IN HEART FAILURE patients is poorly studied and controversial. Thus, Khush and colleagues analyzed the secondary end point in the Treating to New Targets (TNT) study of hospitalization for heart failure. TNT was a study of more than 10,000 patients with stable coronary heart disease (CHD), treated with either 10 or 80 mg/day of atorvastatin, and followed for about 5 years. The primary end point of cardiac death, myocardial infarction (MI), and stroke was reduced 22% by high-dose atorvastatin. A history of heart failure was obtained in 8% of the patients; however, advanced heart failure or an ejection fraction (EF) of < 30% were exclusion criteria. Patients with heart failure had more hypertension, diabetes, peripheral arterial disease, prior MI, and stroke, and were on higher doses of renin-angiotensin-blocking drugs and diuretics. Baseline lipid panels were similar between those with and without a history of heart failure. Lipid/lipoprotein levels were lower in the atorvastatin 80 mg group, except for high-density lipoprotein cholesterol, which was not.

Hospitalization for heart failure occurred in about 3% of the study population; 14% of those with a history of heart failure and 2% of those without. Heart failure portended a poor prognosis. In the atorvastatin 80 mg group, 2.4% were hospitalized for heart failure vs 3.3% in the atorvastatin 10-mg group (P < 0.02). This protective effect was strongest in those with a history of heart failure, but was not different in a variety of other subgroups. One-third of the patients who developed heart failure had angina or MI prior to the event, as compared to 15% overall of patients who did not have heart failure. Hospitalization for heart failure decreased as low-density cholesterol decreased. There was no relation between heart failure and blood pressure.

Khush et al concluded that intensive treatment with atorvastatin in stable CHD patients reduces the incidence of heart failure hospitalization as compared to less intensive treatment, but only in those with a history of heart failure. A reduction in coronary events did not seem to explain the results.

COMMENTARY

Most large-statin trials have excluded patients with heart failure, but interestingly they have shown a reduction in heart failure end points. Small studies of heart failure patients have also shown reduced heart failure end points. This study suggests a benefit in patients with a history of heart failure with high-dose atorvastatin, not low dose. The mechanism of this effect is unclear. The heart failure benefit was associated with lowering LDL cholesterol levels, but those whose LDL decreased were mainly in the atorvastatin 80 mg group, so it could be an effect of high-dose atorvastatin alone.

Since most of the heart-failure hospitalization patients did not have a preceding ischemic event, it is unlikely that an anti-ischemic effect is the mechanism. Other possible mechanisms that have been suggested include increased endothelial function, reduced inflammation, reduced sympathetic tone, and reduced remodeling. There are no data in this study to support any particular mechanism.

One major limitation of the study was that left ventricular function measurements were not part of the protocol. Some patients had a known EF < 30%, but they were excluded. Also, patients with advanced heart failure were excluded, so the results may not apply to them. In addition, evidence of silent ischemia was not sought. Finally, there may have been unrecognized confounders that skewed the results.

Since this was a study of stable CAD patients, it is likely that the plaque stabilization that markedly lowered LDL produces would lead to stabilization or actual improvement in left ventricular function. This is another reason why CAD patients, whatever their lipid profile, should be on statins. As one of my colleagues said of CAD patients, "Whatever their cholesterol is, it is too high for them." ■

Sleep Apnea and Atrial Fibrillation

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

Professor of Medicine, Division of Cardiology, University of Virginia, Charlottesville

Dr. DiMarco is a consultant for Novartis, and does research for Medtronic and Guidant.

This article originally appeared in the April 2007 issue of Clinical Cardiology Alert. It was edited by Michael Crawford, MD, and peer reviewed by Rakesh Mishra, MD.

Synopsis: *Obesity and the magnitude of nocturnal oxygen desaturation, which is an important pathophysiological consequence of OSA, are independent risk factors for incident AF in individuals <65 years of age.*

Source: Gami AS, et al. Obstructive sleep apnea, obesity, and the risk of incident atrial fibrillation. *J Am Coll Cardiol.* 2007;49:565-571.

Gami and colleagues from the Mayo Clinic describe in this paper relationships between obesity, obstructive sleep apnea, and atrial fibrillation (AF). Gami et al identified adult residents living in Olmsted County, Minnesota, who underwent diagnostic polysomnography between 1987 and 2003. Patients with a previous history of atrial fibrillation were excluded. Subjects were defined as having obstructive sleep apnea (OSA) if they had an apnea-hypopnea index during their sleep study ≥ 5. The occurrence of incident AF was timed from the date of the sleep study by querying the Mayo Clinic electronic medical index. Any diagnosis of AF or atrial flutter was made during any medical contact if the occurrence of AF was confirmed by an electrocardiogram was considered an event. Time-to-event analyses were performed using Kaplan-Meier methods to identify univariate predictors of incident AF. The parameters included subject, age, gender, body mass index, relevant comorbidities, OSA status and severity, and physiological sleep variables. Multivariate analyses were performed using Cox proportional hazards regressions methods. Furthermore, in an analysis that included only subjects with OSA, the effect of continuous positive airway pressure after the sleep study was introduced into the multivariate model.

During the period of the study, 3542 subjects underwent polysomnography, and OSA was present in 2626 (74%). After an average follow up of 4.7 years (up to 15 years), incident AF occurred in 133 subjects, for a cumulative frequency of 14%. By univariate analysis, age, male gender, hypertension, the presence of coronary disease, heart failure, a history of smoking, the presence of diabetes, body mass index, obstructive sleep apnea, and measures of the severity of sleep apnea, all were related to the risk of incident atrial fibrillation. There was a significant interaction between OSA and age.

Therefore, Gami et al performed a stratified analysis for subjects younger than 65 years, as well as 65 years or older. Among the subjects less than 65 years old, age, male gender, body mass index, and a history of coronary artery disease independently predicted incident AF. The decrease in nocturnal oxygen saturation was also an independent predictor of incident AF. In contrast, for subjects ≥ 65 years old, only heart failure independently predicted incident AF. In a multivariate regression model that included only subjects with OSA, the use of continuous positive airway pressure did not positively or negatively affect the incidence of AF. In the multivariate regression model, both OSA and obesity independently predicted incident AF.

Gami et al conclude that obesity and the magnitude of nocturnal oxygen desaturation are independent risk factors for incident AF in individuals less than 65 years of age.

COMMENTARY

A number of arrhythmias are commonly seen in patients with organic sleep apnea. This paper shows that atrial fibrillation is strongly related to the presence of OSA. A number of mechanisms may be responsible for this. OSA is associated with diastolic dysfunction, which can lead to increases in atrial size and atrial stretch. Rapid swings in intracardiac pressures can activate atrial ion channels that may contribute to AF initiation. Surges in autonomic nervous system activity may also occur. During OSA-associated bradycardia, atrial repolarization prolongs and, then with elevation of sympathetic activity during apnea catecholamine sensitive ion channels, may lead to increased automaticity. This combination should be a potent mechanism for AF initiation. Finally, OSA has been reported to be associated with systemic inflammation, another potential cause of atrial fibrillation.

It is disappointing that Gami et al cannot demonstrate that the use of continuous positive airway pressure (CPAP) favorably influenced the risk for atrial fibrillation. However, in this study, CPAP was used mostly in the patients with the most severe form of OSA, and a prospective study will likely be required to see if CPAP has a favorable influence on the incidence of AF.

In conclusion, physicians should consider sleep apnea as an important potential cause of atrial fibrillation. Weight reduction and treatment of OSA should be part of the management of AF in patients at risk. ■

CME Questions

4. **Based on the study by Di Tullio and colleagues, an incidentally discovered patent foramen ovale in a patient without a history of stroke:**
   a. significantly increases the risk of ischemic stroke.
   b. significantly increases the risk of pulmonary embolism.
   c. significantly decreases the risk of ischemic stroke.
   d. does not significantly affect the risk of ischemic stroke.
   e. is an indication for stroke prophylaxis with either aspirin or warfarin.

5. **In the observational study by Fagnani colleagues, antithrombotic prophylaxis for patients with cancer and an indwelling central venous device was associated with:**
   a. reduced incidence of catheter-related thrombosis.
   b. reduced risk of death.
   c. increased incidence of pulmonary embolism.
   d. increased incidence of hemorrhagic stroke.
   e. None of the above

6. **Based on the study by Gami and colleagues, independent risk factors associated with the risk of new-onset atrial fibrillation in people under the age of 65 years include:**
   a. magnitude of nocturnal oxygen desaturation.
   b. the use of continuous positive airway pressure (CPAP).
   c. diabetes mellitus.
   d. hypertension.
   e. None of the above

Answers: 4. (d); 5. (b); 6. (a)