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Important Factors in the History, Physical, and Routine Chest Radiograph for Diagnosing Pulmonary Embolism

ABSTRACT & COMMENTARY

Synopsis: *This paper outlines the accuracy of clinical assessment in the diagnosis of pulmonary embolism. A diagnostic algorithm was derived and validated from a study population with suspected pulmonary embolism prior to lung scanning. The diagnostic algorithm included the identification of three symptoms (singly or in combination): sudden onset of dyspnea, chest pain, and fainting and their association with one or more of the following abnormalities: electrocardiographic signs of right ventricular overload, radiographic signs of oligemia, amputation of the hilar artery, and pulmonary consolidations compatible with infarction.*

Source: Miniati M, et al. *Am J Respir Crit Care Med* 1999;159:864-871.

Pulmonary embolism (pe) remains a challenging diagnostic problem. Its clinical presentations are known to be deceptive and nonspecific, which makes clinical diagnosis unreliable. A number of studies have been conducted to provide a diagnostic approach in patients suspected of having PE. More often than not, clinical assessment was correct in excluding PE than in identifying PE. Two prospective studies on the diagnosis of PE, PIOPED and PISA-PED, have corroborated the importance of clinical assessment.[1,2] The results from these studies suggest that physicians' estimates of the clinical likelihood of PE, even if based on history and physical, do have predictive value. However, the characteristics of these estimates have not been described, so there is no way of knowing whether others can replicate these estimates.

The study consisted of 750 consecutive patients with suspected PE enrolled in the PISA-PED. Patients were examined independently by six pulmonologists according to a standardized diagnostic protocol prior to lung scanning. Patients who had abnormal scans required pulmonary angiography. Patients were separated into two groups: the first group of 500 patients was used to derive a diagnostic algorithm and the second group of 250 patients was used to vali-

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date this algorithm. PE was diagnosed by angiogram in 202 (40%) of the 500 patients in the first group. A diagnostic algorithm that included the identification of the following symptoms (singly or in combination) was developed: sudden onset of dyspnea, chest pain, and fainting and their association with one or more of the following abnormalities: electrocardiographic signs of right ventricular overload, radiographic signs of oligemia, amputation of the hilar artery, and pulmonary consolidations compatible with infarction. The above three symptoms (singly or in combination) were associated with at least one of the above electrocardiographic or radiographic abnormalities in 164 (81%) of 202 patients with confirmed PE and in only 22 (7%) of 298 patients without PE. The rate of correct clinical classification was 88% (440/500).

The accuracy of this clinical diagnostic algorithm was then assessed prospectively in 250 patients referred for lung scanning with clinically suspected PE. PE was diagnosed by pulmonary angiography in 104 of the 188 patients with abnormal scans. The overall prevalence was 42% (104/250), which was comparable with the first group of 500 patients. The above three symptoms (sudden onset of dyspnea, chest pain, or fainting), singly or in combination, were associated with at least one of the four electrocardiographic and radiologic abnormalities specific for PE as described above in 87 (84%) of 104 patients with confirmed PE and in only eight (5%) of the 146 patients without PE. The sensitivity and specificity of the diagnostic algorithm were 84% (95% CI: 77- 91%) and 95% (95% CI: 91-99%), respectively. Thus, the rate of correct clinical classification was 90% (225/250).

On the basis of the above diagnostic algorithm, the clinical probability of PE was calculated as high probability (90%), intermediate probability (50%), or low probability (10%). This clinical estimate of PE was then used as a pretest probability to calculate, after perfusion lung scanning, the post-test probability of PE using Bayes' theorem.

For a pretest (clinical) probability of PE of 10%, 50%, and 90%, the calculated post-test probability of PE, conditioned by a lung scan result compatible with PE (PE + scan), was 58%, 93%, and 99%, respectively. For a pretest (clinical) probability of 10%, 50%, 90%, the calculated post-test probability of PE conditioned by a lung scan result not compatible with PE (PE—scan) was 2%, 13%, and 58%, respectively. The present study showed that most patients had concordant clinical and perfusion lung scan findings, so that in most patients, PE could be diagnosed or excluded noninvasively by combining well-defined clinical estimates of PE with perfusion lung scan interpretation. However, if the clinical and perfusion lung scan were discordant, further diagnostic testing was required, including pulmonary angiography or other noninvasive procedures (lower extremity duplex scan, D-dimer test, CT angiography).

COMMENT BY DAVID OST, MD

Numerous studies about PE have been performed in order to come up with systematic diagnostic methods. Clinical manifestations have been investigated, but no single sign or symptom is, in itself, diagnostic of PE. Every approach to PE emphasizes the initial clinical suspicion of PE as being critical in the evaluation of PE, but what constitutes a "high" index of suspicion is not well described.

The diagnostic algorithm developed by Miniati and colleagues includes three relevant symptoms (sudden onset of dyspnea, chest pain, and fainting) that were associated with at least one or more of the electrocardiographic and radiographic findings in greater than 80% of patients with con-

Internal Medicine Alert, ISSN 0195-315X, is published twice monthly by American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

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GST Registration Number: R128870672.

Second class postage paid at Atlanta, GA.

POSTMASTER: Send address changes to ***Internal Medicine Alert***, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $17. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

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Subscription Prices

United States

$199 per year (Student/Resident rate: $100).

Multiple Copies

1-9 additional copies: $100 each; 10 or more copies: $60 each.

Outside the United States

$229 per year including GST (Student/Resident rate: $110 including GST).

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firmed PE. This association occurred in only a few patients in whom the disease had been excluded.

It was a fairly accurate diagnostic algorithm but it failed to identify some 20% of patients with confirmed PE. Miniati et al claimed that in these patients mistakenly classified as not having PE, the severity of the disease was significantly less than those who were correctly diagnosed as having PE.

This study manages to improve the predictive value of the clinical assessment. This diagnostic algorithm may be used as a guideline for clinicians to standardize what constitutes a high index of suspicion. It also highlights for the generalist what factors in the history and physical are most important in evaluating patients with suspected PE. Combining these clinical estimates with the interpretation of V/Q scan should decrease the use of pulmonary angiography. Recent developments in the diagnosis of PE are still being investigated (i.e., CT angiography or MRI) and may be useful in formulating a more specific diagnostic approach for PE, but optimizing the accuracy of the initial index of suspicion will always be important. (*Dr. Ost is Assistant Professor of Medicine, NYU School of Medicine, Director of Interventional Pulmonology, Division of Pulmonary and Critical Care Medicine, Northshore University Hospital, Manhasset, NY.*) ❖

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2. Miniati M, et al. *Am J Respir Crit Care Med* 1996; 154:1387-1393.

Myocardial Perfusion Imaging vs. Troponin I in Acute MI

ABSTRACT & COMMENTARY

Synopsis: *It appears that we still are searching for the optimal tests (and their timing) to predict the major ACS in ED patients with chest pain.*

Source: Kontos MC, et al. *Circulation* 1999;99:2073-2078.

Investigators from the medical college of virginia in Richmond reviewed data from 721 patients who were admitted to the coronary care unit from the emergency department (ED) and who were at low-to-moderate risk for acute coronary syndrome (ACS). The study cohort consisted of patients who had had both early gated rest myocardial perfusion imaging (PI) with 99mTc sestamibi and serial serum cardiac troponin I (cTnI) sampling. The purpose of the study was to compare the sensitivity and specificity of these two diagnostic tests for predicting MI within one week of admission, significant coronary disease on angiography within six weeks of admission, and performance of revascularization (CABG or PTCA).

Of the final cohort of 620 patients, MI was diagnosed in 59 patients (9%) using CK-MB and relative index as the gold-standard criteria. Sensitivity for detecting MI was not significantly different between perfusion imaging (92%) and serial cTnI (90%), and both were significantly higher than the initial cTnI (39%). The specificity for MI was 67% for PI and 96% for serial cTnI. PI identified many more patients than cTnI who subsequently underwent revascularization or who had significant coronary disease. PI had a lower specificity for all end points. Lowering the cutoff value of cTnI from 2.0 ng/mL to 1.0 ng/mL did not significantly change the results.

COMMENT BY STEPHANIE ABBUHL, MD

This is essentially a retrospective study with several design flaws. Only 140 of 620 patients had angiography, leaving the potential for significant bias in conclusions about the end points of significant coronary disease and revascularization. In addition, 71 patients were excluded from the final cohort because only initial cTnI sampling had been done and, therefore, the final sensitivity and specificity calculations to predict all end points may be in error. Despite these limitations, there are some points to be garnered from this study. The low sensitivity to detect MI of the initial cTnI (39%) is a cautious reminder of why we must avoid the temptation to use this single determination to make decisions about admission or discharge for potential MI patients. Kontos and colleagues point out that troponin values may be negative in patients with MI for a number of reasons, including size of the infarct, timing of the sampling (optimal sensitivity is 8-12 hours after onset of necrosis), the threshold for abnormality, and the particular "gold standard" used to define MI.

At first glance, early PI appears promising, with a sensitivity of 92% to predict MI, and the test results were available about three hours after the initial ED evaluation. However, there were many false positives and the cost of PI was not addressed. While Kontos et al conclude that the information from these two tests is complementary, it appears that we still are searching for the optimal tests (and their timing) to predict the major ACS in ED patients with chest pain. (*Dr. Abbuhl is Medical Director, Department of Emergency Medicine, The*

Hospital of the University of Pennsylvania; Associate Professor of Emergency Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA.) ❖

Post-CABG Cognitive Deficits

ABSTRACT & COMMENTARY

Synopsis: *Undoubtedly, additional genetic factors will be found that increase stroke or intrinsic brain deterioration in life's later years. These challenging threats deserve serious consideration and thoughtfully developed prevention.*

Source: Selnes OA, et al. *Lancet* 1999;353:1601-1606.

This informative review states that coronary artery bypass grafting (CABG) as now performed has been remarkably successful in relieving the angina of 94% of survivors for five years. In the United States at least, increasing numbers of inpatients with hypertension, diabetes, and age older than 70 years now safely undergo CABG. Nevertheless, many high-risk candidates suffer from postoperative delirium, memory loss, depression, or stroke.

Although expected perioperative death amounts to only 2-4% following CABG surgery, prospective surveillance indicates that 1.5-5.2% of patients suffer postoperative strokes with a case fatality record of 20%. Cognitive impairment has been reported as high as 10% three months after surgery, with 30% of post-CABG patients complaining of memory defects as late as six months or more. This response may not be specific, however, inasmuch as patients who underwent total knee or hip replacements showed similar postoperative memory defects. Be that as it may, the Hopkins investigation found that some of the post-CABG patients retained space-related deficiencies for five years. Psychological depression following CABG has been emphasized in past investigations, but both Selnes and colleagues and others claim that this occurs only in persons who were preoperatively depressed. Depression, however, fairly frequently follows myocardial infarction and is associated with worse outcomes and increased deaths.

Selnes et al refer to several studies that link preoperative factors to new post-CABG cognitive defects. One report lists the following: increasing age, poor education, and increased cerebral emboli released during cardiac surgery. More chronic factors include diabetes and/or severe arterial sclerosis. Some authors have measured the S100 protein in the spinal fluid as an indicator of post-CABG brain damage, but its specificity remains unsure. Neuron-specific enolase has also been tested in spinal fluid but, again, appears to lack specificity.

COMMENT BY FRED PLUM, MD

Other factors cited as possible causes of post-CABG encephalopathy include the presence of intraoperative hypotension and the amount of intraoperative aortic emboli that become released into the brain. In another study of ancillary risk, Tardiff and colleagues suggest that persons carrying the apolipoprotein E-4 allele may accentuate the risk of precipitating post-CABG dementia.[1] Undoubtedly, additional genetic factors will be found that increase stroke or intrinsic brain deterioration in life's later years. These challenging threats deserve serious consideration and thoughtfully developed prevention. (*Dr. Plum is University Professor, Weill Medical College; Attending Neurologist, New York Presbyterian Hospital.*) ❖

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Alternative Technique for Ring Removal

ABSTRACT & COMMENTARY

Synopsis: *Using ribbon gauze is an effective and a comfortable alternative to the string wrap method.*

Source: Thilagarajah M. *J Hand Surg* 1999;24B:118-119.

Thilagarajah describes another simple, and perhaps more comfortable, technique to remove a ring from a swollen or oversized finger. First, a length of ribbon gauze 1.25 cm in width is passed under the ring. A paper clip can be used to hook the edge as it passes under the band. Next, the gauze distal to the ring is wrapped around the finger, using firm technique and overlapping each turn one-half the width of the gauze. The wrapping continues until the narrower part of the digit is reached. Finally, the proximal end of the gauze wrap is grasped and unwound with a uniform tension simultaneously applied in a proximal-to-distal direction.

COMMENT BY RICHARD HARRIGAN, MD, FAAEM

The above described method is a variation of the

"string wrap method" described in the Roberts and Hedges text.[1] Intuitively, it seems more comfortable and less time-consuming than using string or suture. There are several ways to approach such a problem, the easiest being to lubricate the ring, and the least desirable (from the patient's point of view) being the ring cutter.[1] Other alternatives include the use of 2.0 surgical silk in lieu of string (purported to be less traumatic than string), and the passage of an intact, wide rubber band beneath the ring. The latter method, performed on a lubricated digit, involves subsequently pulling the ring distally while holding both loops, and moving circumferentially around the digit. Thilagarajah reminds us that a digital block may be necessary if the procedure becomes too painful. Whereas I am still awaiting a chance to try this new technique on a real patient, I have found that the gauze technique described above works well on rings that are not stuck. Anecdotally, simple 4×4 gauze is not strong enough; the gauze found in cling wraps seems stronger and better suited. (*Dr. Harrigan is Associate Professor of Medicine, Temple University School of Medicine, Associate Research Director, Division of Emergency Medicine, Temple University Hospital, Philadelphia, PA.*) ❖

Reference

1. Rudnitsky GS, Barnett RC. Soft tissue foreign body removal. In: Roberts JR, Hedges JR. *Clinical Procedures in Emergency Medicine*. 3rd ed. WB Saunders; Philadelphia; 1998:614-633.

The Effect of Epilepsy on Patient Mortality: A Dutch Cohort Study with 40 Years of Follow-up

ABSTRACT & COMMENTARY

Synopsis: *Epilepsy patients have a higher mortality rate secondary to both epilepsy and other related factors.*

Source: Shackleton DP, et al. *J Neurol Neurosurg Psychiatry* 1999;66:636-640.

Shackleton and colleagues, based in the institute for Epilepsy Diagnosis and Management in Heemsteed, the Netherlands, report the outcome of 1355 persons with epilepsy, first diagnosed between 1953 and 1967, and followed until this study terminated in December 1994. Mean age at entry was 19 years with a range of 6 months to 70 years; 746 patients were male, 609 were female, and mean follow-up was 28 years. Sixty percent of initial admissions to the study were younger than 21 years of age. Overall, during the 14 years of patient admissions and the 40 years that the study lasted, 38,665 person years were examined and 404 patients died (normal expected death rate = 128), an increase over expected mortality of 3.2 per 1000. Admission to the Institute's care included a substantial number of patients with symptomatic epilepsy. Accordingly, the mortality rate during patients' first registered treatment year amounted to a high of 16 per 1000 persons. After the first year, the rate declined to 6.9-7.0 times the normal for the ensuing nine-year follow-up. After that, follow-up mortality rates averaged 1.9 in patients living up to the final calculated 25 years of follow-up in the study.

The causes of symptomatic epilepsy in patients dying in the first two years related 19% to brain malignant neoplasms and stroke. After that, those factors fell to 15% of all mortality. Intrinsic epilepsy accounted for 21% of the mortality among these patients throughout the total follow-up study. Road traffic and other accidents averaged 13% of deaths. Overall seven patients, all older than age 20, committed suicide.

During the first two years of follow-up of all entering patients, primary epilepsy carried a 6.8 per 1000 mortality. After two years, this high figure dropped to 3.1 per 1000 and remained there throughout the entire analysis. Uncontrollable seizures may have precipitated such poor outcomes, but respiratory difficulties and/or cryptic acute primary brain disease in children also may have contributed to the remarkably high early rate.

Shackleton et al make several points. Their death rate was higher than those reported in some other series, but most of the latter dealt with an older median age at onset. (As noted above, 60% of all entering patients in this series were < 20 years old.) The death rate was high with epilepsy starting before 20 years, but also within the first years after onset (i.e., ≥ 4 times the rates of subsequent years). Shackleton et al state that other centers have emphasized other primary brain disease as precipitating both death and complications of seizures, but they firmly state that epilepsy itself occupied 21% of their mortality among patients throughout the study. As they emphasize, approximately 1% of newly diagnosed intrinsic epilepsy patients will sooner or later die from the disease. Moreover, in their opinion, "If we also included causes of death indirectly related to epilepsy such as accidental deaths and suicides...the proportion of

epilepsy related death...becomes larger than those deaths related to...malignant CNS neoplasms, cerebral vascular disease, other CNS illnesses."

COMMENT BY FRED PLUM, MD

Shackleton et al take the position that epilepsy resulting from other diseases of the brain importantly contributes to deaths. In their opinion, many of these systemic illnesses also have occurred in patients susceptible to seizures. Their high mortality rate in younger persons perhaps emphasizes that epilepsy, by itself, can importantly be fatal. Regrettably, they don't describe the details of the high mortality rate affecting patients with primary epilepsy during the first two years of their disease. ❖

Pharmacology Update

Rosiglitazone

By William T. Elliott, MD, FACP, and James Chan, PharmD, PhD

The fda has approved smithkline beecham's rosiglitazone for the treatment of type 2 diabetes mellitus. The drug is the second thiazolidinedione to be approved by the FDA. The first drug of this class is troglitazone (Rezulin), which has recently been associated with rare, but highly publicized hepatotoxicity. In clinical trials in about 5000 patients, rosiglitazone has not been associated with drug-induced hepatoxicity or elevation of liver enzymes, but whether rosiglitazone represents a safer thiazolidinedione remains to be established.

Rosiglitazone is marketed as Avandia by SmithKline Beecham and Bristol-Myers Squibb. A third drug in this class, Lilly and Takeda's pioglitazone (Actos), is expected to be approved soon.

Indications

Rosiglitazone is approved for monotherapy, as an adjunct to diet and exercise, to improve glycemic control in type 2 diabetes. It is also indicated for use in combination with metformin when diet, exercise, and either drug alone do not provide adequate control.[1]

Dosage

The recommended starting dose for rosiglitazone is 4 mg daily administered qid or bid. The dose may be increased to 8 mg if there is insufficient glycemic control after 12 weeks of therapy.[1] Higher doses of rosiglitazone tend to be more effective administered twice daily compared to once daily. The difference in glycosylated hemoglobin was significantly greater with 8 mg qid vs. 4 mg bid but not statistically different at 4 mg qid vs. 2 mg bid.[1]

Rosiglitazone may be taken without regard to meals. No dosage adjustment is required in patients with mild to severe renal impairment or in the elderly.[1]

Rosiglitazone is supplied as 2-mg, 4-mg, and 8-mg tablets.

Potential Advantages

Clinical trial results reported no significant difference between placebo in the frequency of ALT elevations more than three times the upper limits of normal (0.2% for both groups).[1] The manufacturer reported no evidence of drug-induced hepatotoxicity in 4598 patients (3600 patient years). However, due to the chemical similarity between rosiglitazone and troglitazone, the FDA is recommending that liver enzymes be checked prior to initiation of therapy and monitored every two months for the first 12 months and periodically thereafter.[1] In vitro data suggest that rosiglitazone does not inhibit any of the major cytochrome P450 enzymes.[1]

Potential Disadvantages

Edema has been reported in 4.8% of patients administered rosiglitazone; thus, the drug should be used with caution in patients with heart failure.[1] Dose-related decreases in hemoglobin (≤ 1.0 g/dL) and hematocrit (≤ 3.3%) have also been reported.[1] Anemia has been reported in 1.9% of patients compared to 0.7% for placebo and 0.6% for sulfonylurea.[1] Mean weight gains of 1.75-2.95 kg were reported in patients treated with 4-8 mg of rosiglitazone for 52 weeks.[1] Rosiglitazone increases LDL-cholesterol mainly during the first 1-2 months of therapy. HDL-cholesterol is also elevated and continues to rise over time. The net result is an increase in the LDL to HDL ratio, which peaks after two months and tends to decrease over time.[1] The FDA's analysis of the data showed an increase in VLDL-cholesterol of 11.5 mg/dL from a baseline of 20.6 after 26 weeks.[7] Contraception may need to be considered in premenopausal anovulatory women with insulin resistance as rosiglitazone may cause resumption of ovulation.[1]

Comments

Rosiglitazone and troglitazone are both members of the thiazolidinedione class of antihyperglycemic drugs. These agents are thought to improve insulin sensitivity

by acting as a potent agonist for the peroxisome proliferator-activated receptor-gamma (PPARg). These receptors are expressed primarily in tissues such as liver, skeletal muscle, and adipose tissue and regulate the control of glucose production, transport, and use.[1] In animal adipose tissue models, thiazolidinedones may act by increasing the number of small adipocytes and decreasing the number of large adipocytes.[2]

Results from clinical trials on the drug have not been published and limited data are available from the manufacturer and/or in abstract forms only.[1,4,5,6,8] In placebo-controlled 26-week studies (n = 1400), rosiglitazone (4-8 mg daily) produced a reduction (difference from placebo) in fasting plasma glucose (FPG) of 31-76 mg/dL in patients with a baseline FPG of 220-229 mg/dL.[1] Corresponding reductions of glycosylated hemoglobin were 0.8-1.5% with baseline values of 8.9-9.0%. Rosiglitazone was generally more effective when administered twice daily compared to once daily.[1] In a 52-week comparative trial (n = 587) with glyburide (mean dose of 7.5 mg/d), rosiglitazone (4 mg bid) produced a mean change from baseline of 41 mg/dL vs. 30 mg/dL in FPG and 0.53-0.72% in glycosylated hemoglobin. Initial reductions in FPG and glycosylated hemoglobin were greater with glyburide; however, values at 52 weeks appeared to be comparable. In contrast to placebo-controlled trials, patients in the active-controlled trial had lower baseline FPG (190-196) and glycosylated hemoglobin (8.07-8.21). Unpublished data indicate that the addition of rosiglitazone to metformin, sulfonyurea, and insulin in type 2 patients has resulted in added improvement in glycemic control.[4-6] Currently only the combination with metformin is FDA approved.

The daily cost of rosiglitazone (4-8mg) ranges from $2.50 to $5 per day. This compares favorably to troglitazone (200-800 mg/d), which ranges from $3 to $9.50 per day.

Clinical Implications

Thiazolidinediones are the newest class of antihyperglycemic agents approved for use in type 2 diabetics. Members of this class, which currently include troglitazone and now rosiglitazone, seem to work by increasing insulin sensitivity. These agents offer a different mechanism of action from the sulfonylureas, metformin, insulin, and acarbose. Thiazolidinediones also offer the potential for combination therapy with these other agents. Toxicity is a concern, with liver toxicity leading the FDA to recently change the labeling for troglitazone. On the other hand, animal studies have suggested that these drugs may protect the vasculature from diabetes-enhanced injury.[3] While clinical trial data are encouraging, whether rosiglitazone will be safer for the liver than troglitazone remains to be determined. ❖

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CME Questions

3. All of the following were true about early perfusion imaging (PI) in the Kontos study of ED patients at low-to-moderate risk for acute coronary syndromes *except*:

a. PI had a sensitivity of 92% to predict MI.
b. PI had a sensitivity very similar to the initial cardiac troponin I.
c. PI had a lower specificity for predicting MI than serial cardiac troponin I.
d. PI results were obtained within about three hours of initial ED evaluation.

4. Preoperative factors linked to post-CABG cognitive defects include:

a. increasing age.
b. diabetes.
c. severe arterial sclerosis.
d. poor education.
e. All of the above

5. In the clinical assessment of pulmonary embolism, which of the following radiographic abnormalities turn out to be specific for PE?

a. Oligemia
b. Platelike atelectasis
c. Right heart enlargement
d. All of the above.

6. Which of the following is not true for rosiglitazone?

a. It raises LDL and HDL cholesterol
b. Higher doses are more effective administered twice a day
c. It has not been associated with liver dysfunction in clinical trials
d. The FDA is not recommending monitoring liver functions when the drug is started.

By Louis Kuritzky, MD

Acute Hyperhomocysteinemia and Reversal by Antioxidant Vitamins

Elevated levels of homocysteine (> 15 micromoles/L) are associated with increased risk of atherosclerotic cardiovascular disease. The mechanisms for this association are not fully understood, but endothelial dysfunction is felt to be a likely culprit.

Homocysteine levels rise after a load of oral methionine in healthy individuals. This study evaluated healthy young men, age 25-45 (n = 20), for the effect of an acute elevation of homocysteine upon endothelial function, as measured by vascular response to L-arginine (the immediate precursor to nitric oxide); endothelial responses were also measured after administration of antioxidants (vitamin E 800 IU and vitamin C 1000 mg) to see whether pretreatment with antioxidants affected outcomes. In addition to vascular responsiveness, plasma lipids, glucose, coagulation profiles, and adhesion molecules were monitored.

Methionine loading produced a change of mean plasma homocysteine from 10.5 to 27.1, unaltered by administration of antioxidants. Coagulation parameters increased significantly upon homocysteine elevation, but this increase was abolished by pretreatment with antioxidant vitamins; the same profile was seen with adhesion molecules. L-arginine normally produces a reduction in blood pressure, platelet aggregation, and blood viscosity. Elevation of homocysteine significantly altered these responses, and the deleterious alterations seen were favorably modified by pretreatment with antioxidant vitamins.

Nappo and associates conclude that acute elevations of homocysteine produce adverse changes in cardiovascular risk profiles, including blood pressure, coagulation parameters, and response to L-arginine. Antioxidant vitamins prevent acute endothelial dysfunction produced by elevation of homocysteine. ❖

Nappo F, et al. JAMA 1999;281: 2113-2118.

Inflammation and Prediction of Diabetes Mellitus in Adults

Macrovascular disease remains the no. 1 cause of mortality in diabetics. Inflammatory processes are felt to play a role in atherosclerosis, and mediators of inflammation such as tumor necrosis factor alfa and interleukin-6 are elevated in type 2 diabetes. The purpose of this study was to determine whether inflammatory markers predict the development of type 2 diabetes in nondiabetic participants in the Atherosclerosis Risk in Communities study (n = 15,792). In this study group, approximately 80% were caucasian and 20% African-American. Inflammatory markers surveyed included fibrinogen, white blood cell count (WBC), sialic acid, orosomucoid, alpha-1-antitrypsin, and haptoglobin, at levels below that which would be considered indicative of an acute inflammatory reaction.

Individuals in the highest WBC quartile had 50% higher odds of developing diabetes. Persons with sialic acid, orosomucoid, and haptoglobin levels higher than the median also had a 1.7-7.9-fold odds ratio for developing diabetes.

Proinflammatory cytokines (e.g., tumor necrosis factor alpha) may affect insulin sensitivity or secretion; it has been theorized that tumor necrosis factor alpha produces insulin resistance by decreasing autophosphorylation of the insulin receptor, in addition to other mechanisms.

Schmidt and colleagues believe that although the pathophysiologic mechanism remains incompletely explained, inflammatory mediators are etiologically involved in the development of type 2 diabetes. ❖

Schmidt MI, et al. Lancet 1999; 353:1649-1652.

Coffee Consumption and the Risk of Symptomatic Gallstone Disease in Men

Numerous aspects of the physiologic effects of coffee and caffeine suggests that coffee ingestion might have some effect on gallstones. Stimulation of cholecystokinin release and enhanced gallbladder contraction are effects of coffee; bile cholesterol concentrations may be affected by cafestol, a component of coffee beans. Caffeine affects bile flow, gallbladder fluid absorption, and tendency to bile crystallization all in an anti-stone-forming fashion.

The cohort evaluated were participants in the Health Professionals Follow-up Study (n = 51,529). Coffee consumption was evaluated on the basis of a 131-item questionnaire in 1986. At the same time, a baseline assessment for presence or absence of gallstones was performed, and surveillance continued through 1996.

More than 1000 cases of gallstone disease were discovered. Intake of regular coffee had a strong inverse relationship with gallstones. For instance, men who drank at least four cups of coffee daily had a 33% lower relative risk of gallstones than those who drank no coffee. No statistically significant relationship was found between consumption of tea, decaffeinated coffee, or caffeinated soft drinks and gallstones. In this population, higher intake of regular coffee in men older than age 40 is associated with reduced incidence of gallstone disease. ❖

Leitzmann MF, et al. JAMA 1999; 281:2106-2112.

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