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INSIDE

LMWHs Appear Equivalent to Unfractionated Heparin for PE

ABSTRACT & COMMENTARY

Source: Quinlan DJ, et al. Low-molecular-weight heparin compared with intravenous unfractionated heparin for treatment of pulmonary embolism. *Ann Intern Med* 2004;140:175.

In this study, the authors performed a meta-analysis of 12 randomized trials comparing the treatment of acute pulmonary embolism (PE) with standard unfractionated heparin (UFH) or one of a variety of low molecular-weight heparin (LMWH) agents. These trials included 1951 patients who were treated for either symptomatic PE or asymptomatic PE in the context of symptomatic deep vein thrombosis (DVT). One thousand twenty-three patients were randomized to receive an LMWH agent and 928 received UFH. Outcomes measured included any recurrent symptomatic venous thromboembolism after treatment and at three months, as well as mortality and bleeding complications. LMWH agents used in these studies included enoxaparin, dalteparin, nadroparin, reviparin, certoparin, and tinzaparin.

In their analysis of the accumulated data, the investigators reported a non-statistically significant decrease in recurrent symptomatic venous thromboembolism at the end of treatment (1.4% vs 2.4%) and at three months (3.0% vs 4.4%) for the LMWH group vs. the UFH group, respectively. In addition, there was no difference in mortality from all causes at the end of treatment (1.4% vs 1.2%) or at three months (4.7% vs 6.1%) for the LMWH and UFH groups, respectively. There also was no difference in rates of major bleeding (1.4% vs 2.3%) or minor bleeding (6.8% vs 5.5%) complications, respectively.

On further analysis, the investigators also found no differences when comparing patients with symptomatic PE vs. those with asymptomatic PE in the setting of DVT in terms of the different treatment arms. Moreover, there was no evidence that any one LMWH agent studied was better or worse than another in terms of efficacy or safety outcomes. Finally, using more advanced statistical methodology such as funnel plotting, the authors report that

their outcomes were not influenced excessively by one study and that there was no evidence of major publication bias, indicating that their findings generalize to all the studies investigated in this meta-analysis.

Based on their findings, the authors conclude that LMWH agents appear to be as efficacious and safe as UFH for the initial treatment of patients with acute PE.

COMMENTARY BY THEODORE C. CHAN, MD, FACEP

LMWH agents have distinct advantages when compared with UFH for the treatment of venous thromboembolism. LMWH agents have a more simplified dosing regimen, allowing administration either once or twice daily. Because of their more predictable pharmacokinetics, routine monitoring of coagulation parameters is not required. As a result, the use of these agents has led to outpatient management of patients with DVT. Because of similar pathophysiology, use of these agents for the treatment of acute PE seems reasonable, and this meta-analysis bears out that such an approach is both efficacious and safe.

The findings of this study, however, must be tempered by the fact that, as a meta-analysis, the results ultimately depend on the quality of, as well as differences between, the 12 studies examined. Moreover, the small number of outcome events (i.e., recurrence, bleeding, and death) means that clinically important differences between LMWH and UFH might not have been detected. Finally, six different LMWH agents were studied, which makes comparison with and selection of a specific agent for clinical use less clear. Finally, while this study indicates that LMWH is at least as efficacious as UFH for the treatment of PE, it did not investigate the potential utility of these agents for outpatient treatment. ❖

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Editorial Group Head: Valerie Loner.
Managing Editor: Allison Mechem.
Marketing Manager: Schandale Kornegay.

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Customer Service: 1-800-688-2421

Customer Service E-Mail Address: customerservice@thomson.com

Editorial E-Mail Address: allison.mechem@thomson.com

World-Wide Web: http://www.ahcpub.com

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Early BNP Measurement Yields More Efficient ED Care

ABSTRACT & COMMENTARY

Source: Mueller C, et al. Use of B-type natriuretic peptide in the evaluation and management of acute dyspnea. *N Engl J Med* 2004;350:647-654.

This randomized, controlled, single-blinded study examined the hypothesis that rapid measurement of B-type natriuretic peptide levels (BNP) would improve the care of patients presenting to the emergency department (ED) with acute dyspnea. Consecutive patients complaining of breathlessness were enrolled in the study, provided they did not have severe renal dysfunction, shock, or trauma. All patients underwent routine evaluation at the treating physicians' discretion. Patients randomized to the BNP group underwent BNP measurement using a rapid assay, and the results were disclosed to the treating physicians. Heart failure was considered unlikely with BNP values less than 100 pg/mL and highly likely with BNP values greater than 500 pg/mL. Clinical judgment and further testing were advised for patients with intermediate BNP values. The authors compared time to discharge, cost of treatment, and mortality between patients in the BNP measurement group and those not undergoing BNP assessment (controls).

Four hundred fifty-two patients were enrolled, evenly split and evenly matched between the BNP group and

the control group. The mean age of subjects was 70 years; half had a history of coronary artery disease, and half had a history of pulmonary disease. Time from ED presentation to final disposition was 63 minutes in the BNP group and 90 minutes in the control group. Fewer patients in the BNP group required admission (75% vs 85%) and fewer required intensive care (15% vs 24%). Among patients requiring admission, those in the BNP group had a shorter median length of stay (8 vs 11 days) and lower hospitalization costs. All these differences were statistically significant. While final diagnosis was heart failure in about half of the patients in each group, exacerbation of chronic obstructive pulmonary disease was diagnosed more often in the BNP group than in the control group (23% vs 11%). Mortality rates were similar in the two groups.

COMMENTARY BY DAVID J. KARRAS, MD, FAAEM, FACEP

BNP is secreted by ventricular myocytes in response to stretch. BNP appears to be a highly useful marker of congestive heart failure and an excellent adjunct to clinical diagnosis in patients presenting to the ED with acute dyspnea. BNP elevation is associated with the presence of heart failure, the severity of heart failure, and patient prognosis.[1] An earlier study found BNP to be a stronger predictor of heart failure in ED patients than any historical, physical, or radiographic finding.[2] BNP has also been shown to be useful in detecting unsuspected heart failure in patients with pulmonary disease.[2]

This study adds to the growing body of literature supporting early BNP assessment in ED patients with dyspnea. While BNP measurement is not a gold standard, this study suggests that incorporating BNP into the work-up of ED patients with dyspnea facilitates confirmation of heart failure or the rendering of an alternative diagnosis (e.g., exacerbation of chronic obstructive pulmonary disease), leading to more efficient evaluations, lower admission rates, and shorter hospital stays. ❖

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3. Maisel AS, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med* 2002;347:161-167.

Vasopressin vs. Epinephrine in Cardiac Arrest

ABSTRACT & COMMENTARY

Source: Wenzel V, et al, for the European Resuscitation Council Vasopressor during Cardiopulmonary Resuscitation Study Group. A comparison of vasopressin and epinephrine for out-of-hospital cardiopulmonary resuscitation. *N Engl J Med* 2004;350:105-113.

From 1999 to 2002, these Austrian investigators randomly assigned adults with out-of-hospital cardiac arrest to receive two injections of either 40 IU of vasopressin or 1 mg of epinephrine, followed by additional treatment with epinephrine, if needed. The primary endpoint was survival to hospital admission, and the secondary endpoint was survival to discharge from the hospital. In all, 1186 patients were analyzed; 589 were assigned to receive vasopressin, and 597 to receive epinephrine. Each group had similar clinical profiles. Cardiopulmonary resuscitation was documented according to the Utstein style. Vasopressin and epinephrine fared similarly when used to treat ventricular fibrillation and pulseless electrical activity. However, among patients with asystole, vasopressin use resulted in higher rates of hospital admission (29.0% vs 20.3 % in the epinephrine group, P = 0.02) and hospital discharge (4.7 % vs. 1.5 %, P = 0.04). Additionally, when vasopressin had no immediate effect, but was followed by additional treatment with epinephrine in asystole patients (n = 732), patients experienced significant improvement in rates of survival to hospital admission and hospital discharge (hospital admission rate 25.7 % for vasopressin plus epinephrine, vs 16.4 % for epinephrine plus epinephrine, P = 0.002; hospital discharge rate 6.2 % vs 1.7 %; P = 0.002). Cerebral performance was similar in both groups.

The authors conclude that the effects of vasopressin were similar to those of epinephrine in the management of ventricular fibrillation and pulseless electrical activity, but vasopressin was superior to epinephrine in patients with asystole. Vasopressin followed by epinephrine may be more effective than epinephrine alone in the treatment of refractory cardiac arrest.

COMMENTARY BY RICHARD HAMILTON, MD, FAAEM, ABMT

Vasopressin, also known as antidiuretic hormone, offers many advantages in cardiac arrest. Vasopressin causes vasoconstriction via peripheral vasopressin receptors, even during hypoxia and severe acidosis.

These effects are greatest in splanchnic, muscular, and cutaneous vessels, while paradoxical vasodilatation is seen in pulmonary, coronary, and the vertebrobasilar circulation. Critical care specialists have used vasopressin in shock resistant to norepinephrine because it increases systemic vascular resistance and decreases cardiac output. This allows for a clinical effect at a lower catecholamine dose. The advantages of a drug of this nature in cardiac arrest in the field are intuitive. This study nicely demonstrates that in the case of asystole, vasopressin may have an immediate effect to restore spontaneous circulation and improve the chances that a patient will survive. Additionally, there may be value in developing vasopressin as a primer drug for making a patient more sensitive to the effects of catecholamine, especially in asystole. Certainly, the place to use this approach is in the field. Frankly, even a small improvement in the chances for patient survival from asystole would be welcome. ❖

Major Trauma and GCS of 3: Do Pupillary Characteristics Give Prognostic Clues?

ABSTRACT & COMMENTARY

Source: Lieberman JD, et al. Use of admission Glasgow coma score, pupil size, and pupil reactivity to determine outcome for trauma patients. *J Trauma* 2003;55:437-43.

The ability to reliably predict fatal outcomes of major trauma patients on arrival to the emergency department (ED) would help to determine the need for further resuscitative efforts, allow for early mobilization of organ procurement agencies, and give the treating physicians the ability to convey accurate information when counseling families. This study from Lehigh Valley Hospital in Pennsylvania sought to determine whether admission Glasgow Coma Scale score (GCS), pupil size, and pupil reactivity are sufficient to predict outcomes of major trauma patients. The authors hypothesized that patients with an admission GCS of 3 as well as fixed and dilated pupils have no reasonable chance of survival to hospital discharge.

This retrospective chart review included all patients older than 14 years admitted to the ED with a GCS of 3. Patients were excluded if they had received paralytics, sedatives, pain medication, atropine, or eye drops in the prehospital setting, or if they had a blood ethanol concentration greater than 100 mg/dL or known drug use prior to injury. Enrolled patients had records reviewed for the presence of fixed and dilated pupils (FD) (defined as pupils greater than 4 mm in diameter bilaterally and nonreactive to light) or absence of fixed and dilated pupils (NFD), survival to hospital discharge, length of hospital stay, resuscitative and surgical procedures performed, discharge destination, and functional status at discharge. For nonsurvivors, data was collected on cause of death and whether or not organ donation occurred.

During the study period, 274 adults were admitted with a GCS of 3. After exclusions, the study group consisted of 137 patients. Of the 137 patients, 104 (63%) had FD pupils and 33 (37%) had NFD pupils. No patient admitted with a GCS of 3 and FD pupils survived to hospital discharge (95% CI 0-3.38%). Of the 46 patients in the FD group who survived their initial resuscitation, almost all died on hospital day one, with all patients dying by hospital day six. Of these 46 patients, 18 (30.5%) went on to organ donation.

In the NFD group, 11 of 33 patients (33%) survived to hospital discharge. The functional status at discharge ranged from complete dependence to complete independence. Nine of the 11 were discharged to rehabilitation facilities, and two to home. Twelve patients survived the initial resuscitation, but died while in the intensive care unit. Of these 12, two (17%) went on to donate organs.

The authors conclude that trauma patients presenting with a GCS of 3 and FD pupils have no reasonable chance of functional recovery. They recommend that these patients may be resuscitated for the possibility of organ procurement. The authors also conclude that for patients with a GCS of 3 and NFD pupils, the prognosis is considerably better.

COMMENTARY BY JACOB W. UFBERG, MD

This study highlights the dismal prognosis of trauma patients presenting to the ED with a GCS of 3 and FD pupils. However, there are several hurdles to clear before we start applying this decision rule to stop the resuscitation efforts for people meeting these criteria. First and most importantly, this study is far too small to realistically place the odds of survival at zero. With only 104 patients in the FD group, the 95% confidence interval for survival ranges from 0 to 3.38%. I would not feel comfortable withholding resuscitation efforts for a patient who may have a 3% chance of survival. A much larger study is warranted.

Also, several of the exclusions would be a problem in implementing this rule for real-time decision making. Many trauma patients already have undergone a major resuscitation effort prior to obtaining the blood alcohol

concentration results. Many other patients would be excluded from this decision rule due to drug use or the possibility of drug use, as the frequency of concurrent alcohol or drug use and major trauma is well known.

However, this study does provide very useful guidance for physicians speaking with family members, allowing for some early risk stratification for discussing prognosis with families. These findings also will help to mobilize organ procurement agencies early, and will help guide physicians when to discuss the possibility of organ donation with families of trauma patients who arrive with a GCS of 3 and FD pupils. ❖

Special Feature

Suspicious Powder Episodes and the ED

By Richard J. Hamilton, MD, FAAEM, ABMT

One weekday morning a few months ago, seven people inside a hotel in downtown Philadelphia were quarantined. Why? A suspicious powder was found in one of the rooms. Fire department personnel, police, and anti-terrorism personnel responded to the 911 call for assistance from the hotel management. An initial on-scene test produced a positive result for anthrax. Traffic was stopped and hotel business came to a halt. Subsequent laboratory testing, plus questioning of the individual who had occupied the hotel room where the powder was found, revealed that it was simply baking soda, used as a substitute for toothpaste. The entire episode lasted more than three hours. No one presented to the emergency department (ED) for medical care in this case, but they have in prior cases—and often with the powdery substance with them. The response of emergency medicine physicians and staff varies from the common sense to the irrational, as individuals struggle to come to grips with dilemmas that protocol and procedure have yet to clarify.

The next time you are in the ED and have a quiet moment, review your hazardous material protocols. Imagine a scenario where, by terror attack, terror hoax, or public fear, an asymptomatic individual (or individuals) brings to you a suspicious powder or substance. Is there a rational approach to handling this situation? Do you understand what emergency personnel mean when they tell you that a "SMART ticket" test was negative or positive? What patients should be tested and by what means? Is decontamination required for everyone? Excellent resources exist, both on-line and in text form, which help to demystify the process behind the response to a potential hazardous material.[1-3]

Field Testing

Field testing generally consists of immunoassay tests. Three basic types of tests serve to detect and measure the binding of antigens highly specific to biological agents: disposable matrix devices (tickets or kits), biosensors that use reagent labels to indirectly assess binding, and biosensors that directly measure substances.[1]

Examples of ticket or kit technologies include the hand-held immunochromatographic assays (HHAs), BioThreat Alert™ (BTA) test strips (Tetracore, Gaithersburg, MD), and the sensitive membrane antigen rapid test (SMART) system. HHAs are similar to urine dipsticks. They provide a qualitative result based on color change, but an experienced observer can detect the strength of the reaction and make quantitative presumptions. Like other dipstick technologies, the quality of the tests improves when an automatic reader replaces the naked eye. BTA test strips use a different approach—lateral flow immunochromatography. This technique provides fewer false positives in environmentally collected samples. Like other lateral flow tests, there is a control reaction as well as variable reaction, and it can be read manually or by a powered reader. This is not unlike the urine pregnancy tests used by most hospitals.

Anthrax and ricin assays are available, and other assays are in development. The ticket system frequently discussed in the media is the SMART ticket. The SMART ticket works by tagging certain antigens with antibodies; positive tests are signified by forming a red dot that is detected by an automated system.[1]

The Centers for Disease Control and Prevention (CDC) does not completely support the use of these hand-held assays. In the case of anthrax, the tests require a minimum of 10,000-100,000 spores to generate a positive result, and they perform best when there are 1 million spores present. Inhalational anthrax requires an inoculation of 8000-50,000 spores. Thus, false negatives and false reassurance from these tests may be of grave concern. However, emergency services personnel often are asked to evaluate large bulk powders. Knowing that 10,000 spores of anthrax takes up a space about the size of a grain of salt, one would assume that sufficient material ought to be present to trigger a true positive. Therefore, even though these tests are not particularly robust, they do have a role in providing the "all clear" for innumerable suspicious-

Table. Decontamination Advisory Clean-up of Suspicious Powder/Substance (Anthrax Concern)

Suspect powder/substance:	Area Decontamination	Personal Decontamination	Medical Evaluation
Is contained in an unopened envelope or container. Human contact only with outside of envelope/container.	None	Wash hands with soap and water.	Not necessary
Has spilled on environmental surface and hands only.	Wash down thoroughly with 1:10 dilution of household bleach (0.5% hypochlorite solution)	Wash hands and forearms with soap and water.	Not necessary
Has spilled on hands, clothes, and environmental surfaces.	Wash down area thoroughly with 1:10 dilution of household bleach (0.5% hypochlorite solution) after approval by law enforcement.	• Wash hands and forearms with soap and water. • Remove contaminated clothing, double-bag and hold for environmental test results. • Take shower with soap and shampoo at earliest opportunity.	Not necessary
Has spilled with massive facial or body exposure, or direct inhalation exposure.	Wash down area thoroughly with 1:10 dilution of household bleach (0.5% hypochlorite solution) after approved by law enforcement.	• Wash exposed skin thoroughly with soap and water. • Remove contaminated clothing, double-bag and hold for environmental test results. • Take shower with soap and shampoo at earliest opportunity.	Refer for medical evaluation if testing of environmental sample is not possible within 24 hours.

Adapted from: The Greater New York Hospital Association, Decontamination Advisory, Clean-up of Suspicious Powder/Substace (Anthrax Concern), New York State Department of Health, 2001. Accessed at www.gnyha.org/pubinfo/nysdoh/anthrax/Decontamination_Advisory.pdf.

powder calls when there is a great quantity of material present. The CDC currently is studying these tests, and guidance should be forthcoming.[2,3]

CDC and the Laboratory Response Network

The CDC and the Laboratory Response Network (LRN) laboratory in your area will employ a two-step process when a sample is submitted. The first generally is an examination of the material for biological weapon characteristics as well as Gram staining. In addition, a polymerase chain reaction (PCR) assay may be employed. Most ED physicians are familiar with PCR assays for chlamydia or gonoccocal infections. In a PCR assay, any sample that contains even a small amount of the target DNA or RNA of bacterial or viral origin can be used. The specimen is collected and placed in a reagent container that liberates the DNA from the cells. Through a specialized protein denaturing and polymerase manufacturing process, the quantity of DNA is amplified. Finally, using a DNA probe, the amplified genetic material is labeled and can be read by an automated device.[2]

The CDC has funded the purchase of platforms for real-time polymerase chain reaction (PCR) assays for the LRN. Currently, the CDC still uses a combination of PCR, culture, and typing methods to identify biological weapons. These assays are being developed for field use, to eliminate transport time and speed identification of suspicious powders. PCRs are not considered final confirmatory evidence, but are highly sensitive and specific across a range of source specimens.[2]

Decontamination Advice

The Greater New York Hospital Association has published some excellent advice for suspicious powders and substances. *(See Table.)* Common sense must prevail at all times; it should be remembered that anthrax is transmitted only by direct skin contact or direct inhalation of aerosolized anthrax spores. These recommendations are not intended for confirmed anthrax contamination.

Conclusion

In anticipation of the next time you are asked to evaluate a patient exposed to a suspicious powder, know which field test your local emergency medical service personnel may be employing, and understand its limitations. Expect field tickets or kits to err on the false-positive side. False negatives are concerning, but theoretically less likely if sufficient material is present and tested. PCR assays available through the CDC and

LRN can require hours to report, but are highly sensitive and specific. ❖

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Physician CME Questions

26. If a suspicious powder is brought to the ED by a patient who carries the substance in a sealed envelope:
- a. the envelope must be burned promptly.
- b. the triage nurse who evaluates the patient must be placed in strict isolation.
- c. regional EMS should be notified to initiate hazardous material testing.
- d. the envelope should be opened cautiously to visualize the material and verify that there is a threat.

27. Which of the following statements is *false* regarding use of B-type natriuretic peptide in ED patients with dyspnea?
- a. Early measurement facilitates identification of non-cardiac causes of dyspnea.
- b. Early measurement facilitates identification of unsuspected heart failure.
- c. Low values (less than 100 pg/mL) exclude the presence of heart failure.
- d. High values (greater than 500 pg/mL) are highly predictive of the presence of heart failure.

28. Trauma patients with an admission Glasgow Coma Scale score of 3 and fixed/dilated pupils have:
- a. a 25% chance of survival to hospital discharge.
- b. almost no hope for functional recovery.
- c. a high rate of survival, but with poor functional status.
- d. no hope to survive long enough for organ donation.
- e. the same survival rate as trauma patients with a GCS of 3 and reactive pupils.

29. In the meta-analysis comparing low molecular-weight heparins (LMWH) with unfractionated heparin (UFH) for the treatment of PE, the study reported that:
- a. LMWH led to increased bleeding risks compared to UFH.
- b. LMWH resulted in a statistically significant lower mortality rate compared to UFH.
- c. LMWH was safe and efficacious for outpatient treatment of PE.
- d. LMWH was equally safe and efficacious for treatment of PE compared to UFH.

30. Vasopressin seems to have greatest benefit in patients with cardiopulmonary arrest and:
- a. asystole.
- b. pulseless electrical activity.
- c. ventricular fibrillation.
- d. ventricular tachycardia.

31. In the study by Mueller et al on the use of B-type natriuretic peptide in patients with acute dyspnea, patients excluded from the study population include those with:
- a. a history of congestive heart failure.
- b. severe renal dysfunction.
- c. severe hepatic dysfunction.
- d. a history of chronic obstructive pulmonary disease.

Answer Key

26. c	**29. d**
27. c	**30. a**
28. b	**31. b**

CME Objectives

To help physicians:
- Summarize the most recent significant emergency medicine-related studies;
- Discuss up-to-date information on all aspects of emergency medicine, including new drugs, techniques, equipment, trials, studies, books, teaching aids, and other information pertinent to emergency department care; and
- Evaluate the credibility of published data and recommendations.

CME Instructions

Physicians participate in this continuing medical education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge.

To clarify confusion surrounding any questions answered incorrectly, please consult the source material. After completing this activity, *you must complete the evaluation form that will be provided at the end of the semester and return it in the reply envelope provided to receive a certificate of completion.* When your evaluation is received, a certificate will be mailed to you.

What's Going On? (Part II)

By Ken Grauer, MD

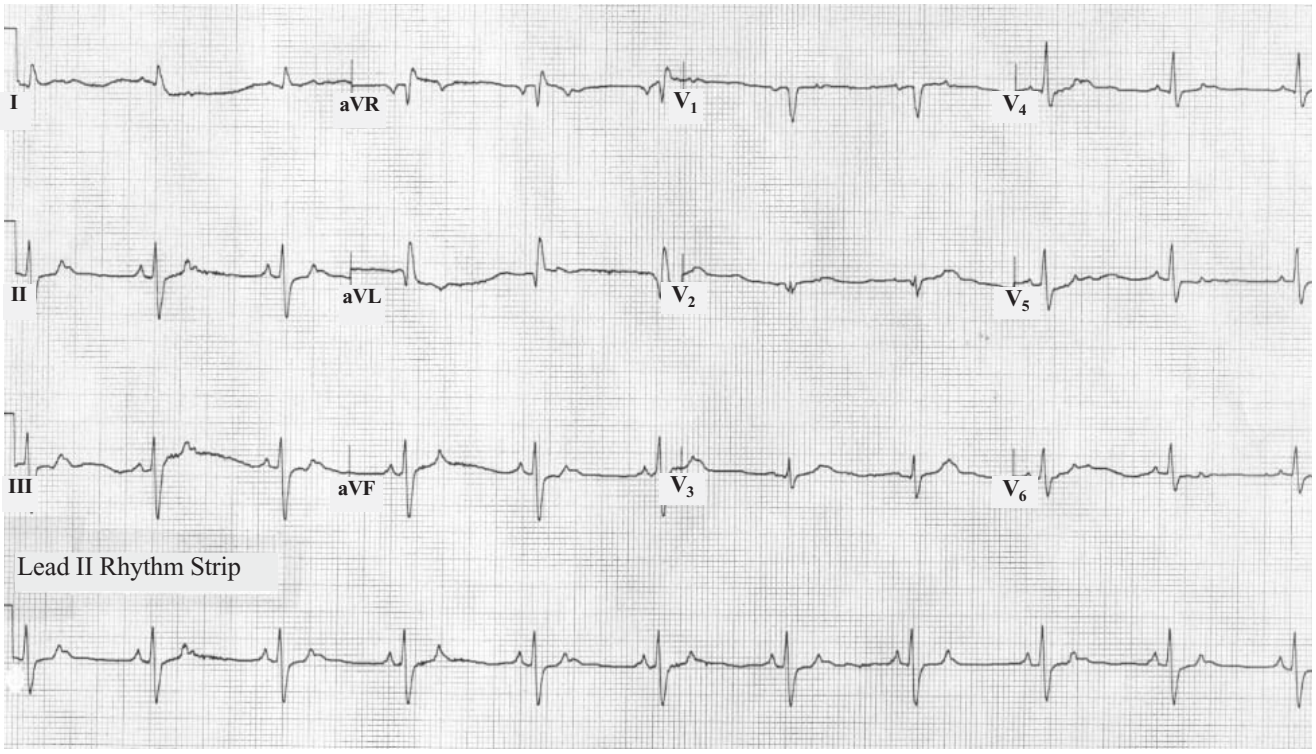

Figure. 12-lead ECG and lead II rhythm strip obtained from an 84-year-old man with acute dyspnea.

Clinical Scenario: The 12-lead ECG and accompanying rhythm strip in the Figure were obtained from an 84-year-old man who presented to the emergency department with acute dyspnea from pneumonia and heart failure. Can you account for the relatively slow heart rate despite his acute shortness of breath? (Hint: As was the case for the ECG review in the March 2004 issue, the key to interpreting this tracing lies within QRST morphology of the lead II rhythm strip.)

Interpretation: QRS complexes occur at a regular rate of about 60 beats/minute in the rhythm strip. However, this is not simply a sinus rhythm. Close inspection of each T wave in the rhythm strip shows variable T wave packaging. This variation in T wave morphology is not the result of artifact. Instead, it represents slight variation in the time of occurrence of premature P waves that deform each T wave. The rhythm is therefore atrial bigeminy, in which each premature P wave occurs so early in the cycle that it is blocked. Thus, the primary problem responsible for the relatively slow heart rate despite this patient's acute dyspnea is atrial bigeminy. Correction of hypoxia and treatment of his heart failure led to the restoration of normal sinus rhythm at a more appropriate rate. ❖

In Future Issues:

CT of the Abdomen After Blunt Trauma: Is Oral Contrast Necessary?