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INSIDE

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How Should We Interpret Pulmonary Crackles?

ABSTRACT & COMMENTARY

By Allan J. Wilke, MD

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Dr. Wilke reports no financial relationship to this field of study.

Synopsis: *Crackles occur commonly in cardiac patients without overt heart failure.*

Source: Kataoka H, Matsuno O. Age-related pulmonary crackles (rales) in asymptomatic cardiovascular patients. *Ann Fam Med.* 2008 May-Jun;6(3):239-245.

PULMONARY CRACKLES (THE PHYSICAL FINDING PREVIOUSLY known as râles, French for "rattle") are commonly sought to confirm a diagnosis of heart failure (HF) and can be fine, medium, or coarse. However, crackles can occur in other diseases (interstitial lung disease,[1] asbestosis,[2] alveolitis,[3] and bronchiectasis[4]) and in presumably normal people.[5,6] Because HF is more frequent as people age, Kataoka and Matsuno wondered about the character of crackles in the elderly with stage A cardiovascular disease, defined as patients "at high risk for HF but without structural heart disease or symptoms of HF".[7] High-risk patients include those with hypertension, atherosclerosis, diabetes mellitus, obesity, or metabolic syndrome or who are taking cardiotoxic drugs or who have a family history of cardiomyopathy. The authors conducted a prospective study at their cardiology outpatient clinic in Japan for fifteen months in 2005-2006. They recruited 385 patients without heart or lung complaints and no history of structural heart disease, decompensated heart failure,

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chronic or recent lung disease, or connective tissue disease. These patients had a physical examination, blood tests, electrocardiogram (ECG), and a chest x-ray (CXR). Patients with a creatinine ≥ 1.2 mg/dL, an abnormal rhythm on ECG, or an abnormal CXR were excluded. The remaining patients had an echocardiogram (ECHO) and a serum B-type natriuretic peptide (BNP), to rule out structural heart disease and HF, and were excluded if the ECHO was abnormal or the BNP ≥ 80 pg/mL. There were 274 patients left after this final screen. They ranged in age from 45 to 95 years (mean 69 years) with men making up 28%. Eighteen percent (18%) had a past or current smoking history. The patients were stratified by age, 45-64, 65-79, and 80-95 years. Ninety-two (34%) had audible-crackles. The incidence of crackles increased with age, 11%, 34%, and 70%, respectively. Older patients were more likely to have bilateral crackles. In 79 (86%) the crackles were fine. Fifty-five patients with audible crackles had chest computed tomography (CT). In 20, the CT was normal and in 27, there were minimal changes noted. For comparison, 19 patients without crackles underwent chest CT. Five of them had minimal abnormalities. In a logistic regression analysis that looked at crackles with age, leg venous insufficiency, leg edema, serum creatinine, and BNP as independent variables; only age was an independent variable. They followed 255 patients for 6 to 12 months (mean 11 months). Congestive HF occurred in 3, acute coronary syndrome in 2, bacterial pneumonia in 5, and interstitial pneumonia in 1.

■ **COMMENTARY**

In this population, audible crackles were fairly common, despite the absence of structural heart disease and symptoms of HF among the patients. This was a large study, but originated in a Japanese cardiology clinic, so the patients may not be representative of your population. This study doesn't tell us what the prevalence of crackles is in the general public, let alone in patients with decompensated HF. Assuming for the moment, however, that the findings are generalizable, how should we incorporate them into practice? Suppose you are examining an at-risk, but asymptomatic, 70-year-old patient who meets the definition of stage A and you hear crackles. The study suggests that this happens approximately a third of the time in patients with no structural heart disease on ECHO and a low BNP. The next step depends on your and your patient's risk aversion. If this were one of my patients whom I trusted to report back, I'd be comfortable following closely. On the other hand, if this were a new patient or one who didn't always return for follow-up, I'd order an ECHO and a BNP. ■

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For the Record…

ABSTRACT & COMMENTARY

By Barbara A. Phillips, MD, MSPH

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Dr. Phillips reports no financial relationship to this field of study.

Synopsis. *As of early 2008, a minority (about 17 %) of physicians have a basic or extensive electronic health record (EHR) system. Those who use electronic health records believe they improve the quality of care, and tend to be primary physicians, those practicing in large groups, hospitals or medical centers, and located in the western region of the US.*

Source: DesRoches CM, et al. *NEJM.* 2008;359:50-60.

THIS GROUP OF HEALTH POLICY LEADERS SOUGHT TO learn the proportion of physicians who are currently

using electronic health records, whether they were satisfied with the systems they used, and what impact the physicians believe that these systems have on quality of patient care. They developed a survey with extensive consultation from experts in survey research, health information technology, and health care medicine, and in conjunction with physician and hospital groups. They defined a "fully functioning" electronic health record as one that 1. records patients' clinical and demographic data; 2. views and manages laboratory and imaging tests; 3. manages order entry (including electronic prescriptions); 4. supports clinical decisions (including warnings about drug interactions). For purposes of this survey, they also defined a "basic" electronic health record, which differed primarily from the fully functioning system in that it did not support all order-entry capabilities or provide clinical decision support.

They randomly selected 5000 physicians from the 2007 Physician Masterfile of the American Medical Association (AMA), and excluded those for whom it was impractical or inappropriate to administer this survey (eg, those who were retired, physicians in training, and those in federally owned hospitals). The survey was administered by RTI through direct mail between September 2007 and March 2008. The survey response rate was 62%. Respondents were 75% male, 77% white, 47% primary care, 83% urban. We are not told much about the ages of the respondents, but 59% of them had been in practice 20 or more years.

Overall, 17% of respondents reported having an electronic health record system, with only 4% reporting use of a fully functioning system. For those with a fully functional system, 71% reported that it was integrated with the electronic record system at the hospital(s) where they work. Among the 83% majority of respondents not using an electronic health system, 42% reported that their practice had either already purchased or had plans to purchase a system within the next 2 years.

Those who used electronic health systems tended to be younger, worked in large or primary care practices, worked in hospitals or medical centers, and lived in the western U.S. Rates of use did not vary by payer or patient ethnic mix. The most commonly-used function for both fully functioning and basic systems was to allow patients to request refills for prescriptions online. The most common prompt from electronic health systems was to alert the physician to a critical laboratory value, with preventing drug allergic reaction a close second. Physician satisfaction with electronic health records was high, especially with regard to the systems' ability to enhance communication with other providers, afford timely access to records, avoid medication errors, and refill prescriptions. Those who had fully functional systems tended to be more satisfied (93%) than those with basic systems (88%).

Physicians who did not have access to electronic health record systems cited capital costs (66%), finding a system that matched their needs (54%), uncertainty about return on investment (50%), and concern that the system would become obsolete (44%). Conversely, the factors that were most frequently cited as enhancing adoption were financial incentives for the purchase and payment for use of an electronic-records system. Protection of physicians from personal liability for record tampering by external parties was also mentioned by many as a potential facilitator of adoption.

■ COMMENTARY

First of all, when did "electronic medical records (EMR)" become electronic health records? The terminology has recently changed, reflecting our culture's subtle switch in emphasis from "medical care" to "health care." Whatever you want to call it, the electronic health record has been slow to flourish in this country, with only 17% of a representative sample of physicians reporting access to such systems in the current study. This estimate is in line with those of previous smaller studies,[1-3] and supports the notion that the capital cost of implementing such systems is daunting. In 2006, the National Ambulatory Medical Care Survey (NAMCS) found that 9.3% of respondents reported using systems similar to the basic electronic record as defined in the current study;[4] thus, the authors of the current study cautiously speculate that the use of electronic health records may be increasing slowly. Indeed, 42% of respondents in the current report have immediate plans to implement electronic health systems. Although physicians are notoriously resistant to change, those who have access to electronic health systems report high levels both of use and of satisfaction with these systems, and fully functional systems tended to be scored more highly than basic systems.

The size of the group (an indirect predictor of resources) is a critical factor influencing the adoption of electronic health records in this and other studies; in the current study, groups with 50 or more physicians were much more likely to have electronic records systems than were smaller groups. Further, the physicians in this study who do not yet have electronic health records overwhelmingly listed cost as

the primary barrier.

The slow adoption of electronic health records in the U.S. lags behind that of many Western industrialized nations, where more than 90% of primary care physicians use electronic records in their offices.[5] Other countries have used a variety of public and private incentives to encourage adoption of electronic records. Help may be on the way for physicians in the U.S.; Centers for Medicare and Medicaid Services has recently proposed incentives for adoption of health information technology by physicians in order to increase its use.[6]

My own experience with electronic health records has largely been at a Veterans' Administration (VA) hospital. Although the initial learning curve is steep and painful, the ease and timeliness in communication and reduction in potential errors is remarkably improved.

The current paper suggests that we have a long way to go, but we are definitely on the way, and that making the transition will be worth it. ■

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Fatigue—Can It Be Due To Cardiac Malfunction?

ABSTRACT & COMMENTARY

By Harold L. Karpman, MD, FACC, FACP

Clinical Professor of Medicine, UCLA School of Medicine

Dr. Karpman reports no financial relationship to this field of study.

Synopsis: *Complaints of fatigue were not associated with changes in blood pressure or heart rate but were significantly associated with decreased cardiac index and stroke index even after controlling for demographic variables and depressive symptoms.*

Source: Neleson R, et al. *Arch Inter Med.* 2008;168(9): 943-948.

FATIGUE IS ONE OF THE MOST COMMONLY ENCOUNtered complaints in medical practice, especially in the elderly. It is frequently accompanied by a decreased capacity or motivation for work activities and by feelings of weariness and sleepiness. It is a non-specific symptom commonly associated with medical conditions such as obstructive sleep apnea, hypothyroidism, anemia, infections, renal or hepatic disease, heart failure, severe stress, chronic fatigue syndrome and/or a variety of other medical or surgical conditions. Patients with severe chronic fatigue syndrome have been shown to have significantly lower stroke volumes (SV) and cardiac output (CO) than the control patients.[3,4] Individuals who reported more sleepiness were found to have lower CO and significantly lower SVs and furthermore, increased sleepiness has even been found to be related to decreased CO in a sample of patients with obstructive sleep apnea but without known cardiac disease.[5]

Because fatigue occurs with and without other symptoms which have been demonstrated to be associated with hemodynamic cardiovascular malfunction, Neleson and his colleagues mounted a study to examine the relationship between self-reported fatigue and hemodynamic functioning at rest and in response to a stressor (ie, public speaking) in healthy individuals.[10] Heart rate, SV and CO were measured using impedance plethysmography in a total of 142

individuals at rest and during a speaking stressor. SV and CO were converted to stroke index (SI) and cardiac index (CI) by adjusting for body surface area. Those study participants complaining of excessive fatigue demonstrated lower SI and CI levels than did individuals with moderate and minimal fatigue both at rest and in response to the speaking stressor suggesting that the fatigue may have been, at least in part, secondary to hemodynamic cardiovascular abnormalities even in ostensibly healthy individuals.

■ COMMENTARY

Subtle hemodynamic changes in SI and CI had been noted to occur in veterans with Gulf War Syndrome and even in reasonably healthy individuals who complain of chronic fatigue.[3,4,6-9] These findings suggest that fatigue is often associated with a weak but measurable relationship with cardiac malfunction as determined objectively by altered measurements of CI and SI. However, simple office measurements such as heart rate or blood pressure are rarely significantly altered only by fatigue and therefore, these simple measurements on the usual office patient are rarely abnormal enough to explain significant fatigue in that patient. The results of the Neleson study[10] should be interpreted with caution because of the small number of patients in the trial and because impedance cardiography tends to underestimate the true SI and CI; in fact, other techniques such as echocardiography should be considered for any future studies which may be mounted to evaluate hemodynamic abnormalities associated with complaints of fatigue.

In summary, the results of the Neleson study[10] suggest that decreased hemodynamic functioning (ie, decreased CI and SI) may be related to complaints of fatigue at rest and during acute stress even in apparently healthy subjects. It should be recognized that the effects of fatigue and/or stress on cardiovascular functioning as observed in this study may even be more significant in patients with known cardiovascular disease (ie, for example, some studies suggest that excessive fatigue may be an early manifestation of heart failure[1, 2]) and therefore, the abnormal hemodynamic effects observed in patients with fatigue may also explain the beneficial response observed to occur on both cardiovascular conditioning and on symptoms of fatigue with exercise.[11, 12]). Since so many studies have demonstrated the solid benefits of regular exercise in cardiac patients, it would seem that there would be little to lose by extending the benefits of exercise to healthy individuals as well as to cardiovascular patients complaining of fatigue since hemodynamic abnormalities secondary to fatigue may be at least partially responsible for the fatigue in both groups of patients. ■

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Pharmacology Update

Dutasteride Capsules (Avodart®) Plus Tamsulosin (Flomax®) for BPH

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

Dr. Elliott is Chair, Formulary Committee, Northern California Kaiser Permanente; Assistant Clinical Professor of Medicine, University of California, San Francisco; Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA.

Drs. Chan and Elliott report no financial relationship to this field of study.

THE FDA HAS APPROVED THE COMBINATION OF dutasteride and tamsulosin for the treatment of symptomatic enlarged prostate. Dutasteride is a 5-alpha reductase inhibitor that reduces prostate volume by blocking the conversion of testosterone to dihydrotestosterone leading to epithelial atrophy. Tamsulosin is an alpha-adrenergic receptor blocker that reduces smooth muscle tone in the prostate and bladder neck. Both products have been previously approved as monotherapy for benign prostatic hyperplasia.

Indications

Dutasteride is indicated for use in combination with tamsulosin for the treatment of symptomatic benign prostatic hyperplasia (BPH) in men with enlarged prostate.[1]

Dosage

The recommended dose is dutasteride 0.5 mg once daily with tamsulosin 0.4 mg daily. Tamsulosin should be taken 30 minutes after the same meal every day.

Potential Advantages

The combination provides greater benefit than monotherapy with tamsulosin or dutasteride alone in improving urinary symptoms, quality of life, and peak urinary flow in men with symptomatic BPH.[1,2]

Potential Disadvantages

The combination also combines the adverse events of both agents. Sexual dysfunction (eg, erectile dysfunction, impotence, decreased libido, ejaculation disorder) and nipple pain have been associated with dutasteride.[1,2] Orthostatic hypotension, headache, and dizziness have been associated with tamsulosin.

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CME Objectives

The objectives of *Internal Medicine Alert* are:

- to describe new findings in differential diagnosis and treatment of various diseases;
- to describe controversies, advantages, and disadvantages of those advances;
- to describe cost-effective treatment regimens;
- to describe the pros and cons of new screening procedures.

Comments

The approval of combination therapy was based on the 2-year results of an ongoing study, Combination of Avodart and Tamsulosin (CombAT).[1,2,3] This 4-year, double-blind, multicenter study enrolled 4838 male subjects 50 years of age and older, with moderate-to-severe symptoms, with prostate volume of 30 cm^3 or larger, and PSA of 1.5 ng/ml or higher. Subjects were randomized to tamsulosin (0.4 mg), dutasteride (0.5 mg), or the combination once daily. The primary endpoint was change in the International Prostate Symptom Score (IPSS). This is identical to the American Urological Association Symptom Index (AUA-SI) with the addition of a quality of life question. The 4-year endpoints were timed to BPH-related surgery or acute urinary retention. Secondary endpoints included change in prostate volume and peak urinary flow. At 2 years, the combination showed a significant improvement of IPSS over dutasteride (after 3 months) and tamsulosin (after 9 months) and improvement in BPH-related quality of life (after 3 and 12 months respectively) as well as improved peak urinary flow from baseline (after 6 months).

Adverse events were more frequent in the combination regimen. CombAT is the second large study involving a 5-alpha-reductase inhibitor with an alpha-adrenergic blocker. The Medical Therapy of Prostate Symptoms (MTOP) trial randomized 3047 male subjects to finasteride, doxazosin, and the combination.[4] That study concluded that the combination was more effective in reducing the risk of composite clinical progression (eg, ≥4 point increase in AUA-SI, acute urinary retention, renal insufficiency, recurrent urinary tract infection, or urinary incontinence). However, the difference between the combination and doxazosin in terms of symptoms was not statistically significant at 1 year.[4] The findings also suggest that men with larger prostates and higher PSA gained more benefit. In CombAT, the subjects had larger prostate volume (mean of 55 ± 23.4 cm^3 vs 36.3 ± 20.1 cm^3) and higher PSA value (4.0 ± 2.06 ng/ml vs 2.4 2.1 ng/ml). It is not known if the combination of any 5-alpha reductase inhibitor and any alpha-adrenergic receptor blockers would achieve the same therapeutic effect. Dutasteride is an inhibitor of type 1 and type 2 while finasteride inhibits type 2 isoenzyme only. Similar prostate volume reduction has been reported with the two drugs.[5] Compared to other alpha-blockers tamsulosin and alfuzosin are more selective for the receptors in the genitourinary tract.

Clinical Implications

The combination of dutasteride and tamsulosin has been shown to benefit patients with larger prostate volume and higher PSA levels. Currently, the American Urological Associate recommends combination therapy for men with symptoms and demonstrably enlarged prostate glands.[6] ■

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CME Questions

27. In an asymptomatic patient at risk for heart failure, but without structural heart disease, the presence of pulmonary crackles:

a. clinches the diagnosis of heart failure.
b. decreases with age.
c. predicts an abnormal echocardiogram.
d. predicts a serum B-type natriuretic peptide > 80 pg/mL.
e. occurs 34% of the time.

28. As of early 2008, use of electronic health records by physicians in the United States was

a. about 80%
b. about 60%
c. about 40%
d. about 20%

Answers: 27 (e); 28 (d)

By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville
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Sublingual Immunotherapy

Allergic rhinitis is often treated successfully with antihistamines and local corticosteroids, but because of inadequate symptom control, patient preference, or both, sometimes allergen desensitization becomes preferable. Most of our knowledge about desensitization comes from studies using parenteral allergens, but other routes for desensitization have been suggested. Sublingual immunotherapy (SIT) has been recently demonstrated in large double-blind, placebo controlled trials to be effective in reducing allergic rhinitis symptoms and need for rescue medication.

The exact mechanism by which parenteral immunotherapy produces its beneficial effects is still controversial, since treatment induces T regulatory cells that blunt the late-phase reaction, generates IgG "blocking" antibodies to offending antigens, and decreases the IgE response to antigens. Because SIT provides antigen in sufficient magnitude that some is absorbed through the oral vasculature, stimulation of regional lymph nodes to produce allergen-specific IgG has been demonstrated.

Advantages of SIT include that desensitization may be initiated at a full maintenance dose (as compared to injections, which must be very gradually titrated), the very low likelihood of anaphylaxis (as demonstrated by trial data to date), and lack of necessity for injections, which may be preferred by some patients, especially children.

Disadvantages of SIT include limitations of approved antigens (thus far, grass allergens are the only ones commercially available, and none are yet FDA approved), limited data-base compared with injection immunotherapy, and especially the uncertainty surrounding durability of SIT, since long term trials of SIT (beyond 2 years) are lacking.

For patients with compelling reasons to seek SIT instead of injection, SIT is available in England. ■

Frew, AJ. N Engl J Med. 2008;358:2259-2264.

Methylnaltrexone for Opioid-Induced Constipation

Of the adverse effects induced by opioid therapy, constipation is singular in its persistence. Opioid-induced bowel dysfunction (OBD) is felt to result primarily from action of opioids upon the mu receptor in the colonic myenteric plexus, resulting in lack of contractility of the longitudinal muscle fibers, and hence a loss of peristalsis. Traditional laxative tools for constipation are generally employed with some success. Bulk forming laxatives (eg, fiber), should be avoided in OBD, since they may actually worsen symptoms or even lead to full obstruction in a non-motile colon.

Methylnaltrexone (MTX) is a mu-receptor antagonist which, because it is a quaternary amine compound, does not induce withdrawal symptoms in persons on chronic opioid therapy. Small pilot trials have supported the utility of both oral and parenteral MTX for prompt relief of constipation.

Thomas, et al studied a population of subjects on opioid therapy (n=133) who had not achieved relief of constipation with "traditional" laxatives. MTX subcutaneous was administered every other day for two weeks. Within 4 hours of the first dose, almost half of subjects had a spontaneous bowel movement (ie, without the use of a "rescue" laxative). Pain scores were not adversely affected, and there were no signs of opioid withdrawal. No serious adverse events attributable to MTX were seen. ■

Thomas J, et al. N Engl J Med. 2008;358:2332-2343.

Prucalopride for Severe Constipation

Chronic constipation sufferers have few FDA-approved therapeutic choices since the removal of tegaserod from the market due to CV toxicity. Mechanistically similar to tegaserod, prucalopride (PRU) is a 5-HT4 receptor agonist; dissimilar to tegaserod, PRU does NOT interact with receptors putatively associated with cardiovascular risk.

A double-blind trial of PRU in severe constipation randomized patients to 2-4 mg/d of oral PRU x 12 weeks or placebo (n=620). Entry criteria included having < 2 spontaneous bowel movements (SBM) per week; indeed, 75% of study subjects had < 1 bowel movement per week.

Thirty-one percent of PRU-treated subjects (2 mg dose) reported three or more SBM per week, vs 12% of the placebo group. Other problematic attributes of constipation (eg, straining at stool, consistency of SBM) were statistically improved also. Treatment was rated as quite-extremely effective in 33.3% of PRU 2 mg subjects (vs 17% placebo).

No serious adverse effects were seen. Diarrhea was seen in 13.5% of patients at the 2 mg dose (vs 5.3% placebo). PRU shows promise as a treatment for chronic severe constipation. ■

Camilleri M, et al. N Engl J Med. 2008;358:2344-2354.

In Future Issues: Atrial Fibrillation and Heart Failure