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INSIDE

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Breast Size Not All It's Stacked up to Be

ABSTRACT & COMMENTARY

By Allan J. Wilke, MD

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

Synopsis: *Bra cup size at age 20 predicts risk of diabetes mellitus in later life.*

Source: Ray JG, et al. Breast size and risk of type 2 diabetes mellitus. *CMAJ.* 2008;178:289-295.

The Nurses' Health Study 2 began prospectively gathering data on 116,609 women in 1989. Along with providing the usual information about demographics, anthropomorphic data, health and lifestyle, these women were asked for their heights and weights at age 18 (to calculate body mass index [BMI]) and for their brassiere cup size (BCS) at age 20. They were also asked to estimate their body fat in childhood (BFC) by selecting from drawings that pictured what they looked like between the ages of 5 and 10 years. After excluding women who were already known to be diabetic or who developed gestational diabetes or who did not report BCS or BMI, the researchers had 92,106 women with complete datasets. Most of the women were white and at baseline the average age was 38. They were similar with respect to cumulative months of lactation, diet, multivitamin use, and amount of vigorous exercise. The women were placed in BMI quintiles (≤ 18.8, 18.9-20.1, 20.2-21.2, 21.3-23.0, and ≥ 23.1) and four bra cup size groups (≤ A, B, C, ≥ D). As BCS increased, so did BMI, waist circumference (WC), and BFC. Age of menarche was inversely related to BCS. Family history of diabetes mellitus (DM) and personal history of smoking were more frequent as BCS increased. Regarding the primary endpoint of this study, during 886,443 person-years of follow up (9.6 years on average), 1844 (2%) women developed DM. Compared to women in the

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first quintile, women in the fifth quintile had an age-adjust hazard ratio of 5.05 (95% confidence interval [CI] 4.29-5.95). Women who wore a D-cup at age 20 had worse diabetic outcomes than women who wore an A-cup. DM occurred 2.1 years earlier and the age-adjusted hazard ratio was 4.99 (CI 4.12-6.05). Adjusting for BMI at age 18, current BMI, and WC attenuated the risk to 1.58 (CI 1.29-1.94), which was still statistically significant. Although for several of the twenty BCS/ BMI combinations there were too few cases of DM to be statistically significant, there was a general trend within each BMI quintile for an increase in the hazard ratio with increasing BCS.

COMMENTARY

The conclusions of this study are biologically plausible. Elevated BMI[1] and abdominal obesity[2] are risk factors for type 2 diabetes mellitus. Obesity in childhood predicts age of thelarche and breast size.[3] The interaction of BCS and BMI suggests a dose-response relation and indicates that the two measures are independent of one another. Using the same database, BCS is also associated with premenopausal breast cancer.[4] Insulin-like growth factor is expressed in breast tissue.[5] Since this is a cohort study and it doesn't show cause and effect, the question remains, "Do large breasts (primarily composed of endocrino-active adipose tissue) predispose to the development of diabetes or is there some underlying metabolic defect that leads to obesity, large breasts, and diabetes?"

A more practical question is, "Should bra cup size at age 20 be a vital sign?" This has its attractions. It doesn't involve any actual measurements (although the article spends a paragraph describing the official procedure); your patient can just tell you. I performed an informal survey of my wife, adult daughters, and some women coworkers. None were embarrassed and all but one claimed to remember. Recall bias is an obvious concern, but recording the data prospectively should reduce that.

The correlation between BCS and smoking puzzles me. Is the reasoning that women with larger BCS are more likely to have larger BMIs (which is true according to this study), and that these women were smoking in an attempt to lose weight? It may be a follow-up question to ask your female patients. The combination of diabetes and smoking is particularly dangerous.

This study's chief strengths are its large size and its prospective design. Recall bias is its main limitation. The BMI quintiles seem overweighed to the lower end; the fifth quintile includes people who are not obese (BMI < 25). Further division may have demonstrated that women with a BMI of 26 fare better than women with a BMI of 30, but the differences in the hazard ratios for the fourth and fifth quintile were already great.

In a commentary in the same issue,[6] Dr. Sorisky reviews the current state of knowledge about adipose tissue and suggests that we should call it FAT (functional adipose tissue). He then discusses dysfunctional adipose tissue. I recommend it as an easy and informative read. Our understanding of FAT has advanced way beyond white and brown! ■

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Hypertension in the Emergency Department: Should We be Concerned?

ABSTRACT & COMMENTARY

By Joseph Varon, MD, FACP, FCCP, FCCM

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

Synopsis: *Patients that present with elevated blood pressure (BP) to the emergency department (ED) frequently have elevated BP measurements at home, independent of pain and anxiety. Clinicians must provide close follow up for these patients.*

Source: Tanabe P, et al: Ann Emerg Med 2008; 51: 221-229.

This prospective cohort study was aimed at evaluating those patients without a prior history of hypertension that presented to a single urban ED and were found to have BP of at least 140/90 mm Hg. These patients were then provided with automatic BP monitors and instructed to take their BP at least twice a week for a period of one week. The data obtained in the ED and at home was correlated with the Spielberg State Anxiety State (SSAS) scale and a 10-point pain scale. The change in BP upon discharge from the ED was also recorded and used for the analysis.

Two hundred sixty-one patients met study criteria characteristics and were offered enrollment in this study. Of them, 189 were enrolled (mean age was 47 ± 13 years). Fifty percent were 50% women, 35% African Americans, 60% Caucasians and 7% Hispanic. Of the patients enrolled, 83% (n=156) returned the monitor and completed a minimum of 4 BP readings. The mean number of BP readings was 14.

Of the 156 patients who returned the monitor and completed BP recordings, 51% had increased mean home BP readings. Of these patients with elevated BP, 71% had increased systolic and 88% had increased diastolic BP. The mean BP difference from ED to home was 19.5 mm Hg systolic and 3.6 mm Hg diastolic. Interestingly in this cohort, a high proportion of patients reported having commercial insurance.

Those patients with increased home BP readings tended to be older, were more likely to be women, and more likely to be African American and had significantly higher ED systolic BP measurements. The mean pain score for the cohort was 4.1 and the mean anxiety score was 37.8. Anxiety was not correlated with a change in either systolic or diastolic BP. No association was found either with the presence of pain in the ED in those patients with persistently elevated BP readings at home.

COMMENTARY

It is estimated that there are more than 70 million adults in the United States with hypertension.[1] Roughly 1 out of 100 patients with essential hypertension will experience a hypertensive crisis at some point during their lifetime, and these hypertensive emergencies and urgencies account for more than 27% of all acute medical problems presenting to EDs in the United States.[2] What it is not known, is the relevance of isolated BP elevations in the ED for those patients with prior history of hypertension.

The study by Tanabe and associates is interesting because it shows that patients with elevated BP in the ED in more than 50% of the cases continued to have elevated BP at home.[3] Moreover, this persistent elevation in BP was independent of pain or anxiety. This may be a good indicator for hypertension and clinicians working in EDs should arrange for adequate follow up of these patients. ■

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Reflexology Might Help Treat Detrusor Overactivity

ABSTRACT & COMMENTARY

By Frank W. Ling, MD

Clinical Professor, Dept. of Obstetrics and Gynecology, Vanderbilt University School of Medicine, Nashville

This abstract originally appeared in April 2008 OB/GYN Clinical Alert

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

Synopsis: *Foot reflexology was more effective than nonspecific foot massage in reducing daytime urinary frequency.*

Source: Mak HL, et al. *Int Urogynecol J Pelvic Floor Dysfunct.* 2007;18:653-658.

One hundred and twenty subjects with symptoms of idiopathic detrusor overactivity (OAB)

were recruited to evaluate the efficacy of reflexology compared to nonspecific foot massage. Ten therapists were trained in a standardized fashion, and each treated the same number of patients in each group. Patients kept voiding diaries for 3 days before and after the therapy. They were randomized to one group or the other and were also asked whether they thought they were in the reflexology group or the control group. Ninety-seven of the 120 patients completed the study. Reduction in daytime micturition frequency was seen in both groups with the reflexology group showing a greater decrease (1.9 vs 0.55 episodes, $p = 0.029$). Urge incontinence episodes was also decreased in both groups, but did not reach statistical significance (2.18 vs 1.04, $p = 0.055$). Nocturnal micturition frequency, urgency episodes, and pad utilization were not changed in either group. Quality-of-life measures were similar in the two groups. Interestingly, significantly fewer patients in the foot massage group believed that they had true reflexology.

COMMENTARY

So how far "out there" is foot reflexology in your practice? Without question, it is not utilized to the same extent in different parts of the country, or world for that matter. This study was done in Hong Kong. Some readers with a good memory may recall that a very nice randomized, placebo-controlled trial demonstrating the potential efficacy of reflexology for premenstrual syndrome was published in *Obstetrics and Gynecology* by Oleson in December of 1993. In that case, their control group received "sham reflexology," not dissimilar to what was done here. The study was done in California. I can assure you, however, that alternative therapies are everywhere (including where I practice in Memphis, Tennessee). They just aren't discussed and/or utilized so openly in some regions.

In this study, the authors went to great lengths to make this a scientifically sound endeavor. They excluded patients appropriately, and went to great lengths to standardize the therapy, be it true reflexology or nonspecific foot massage. This included using the same creams and controlling the topics of conversation during the therapy. Despite their best efforts, a significantly greater proportion of the control group felt that they had not received the true treatment. This demonstrates that true blinding was not achieved in this study and how difficult this can be.

Theoretically, reflexology's benefit stems from areas of the foot and hand corresponding to other glands, organs or areas of the body. It is unclear what the true mechanism is that creates the benefits that patients report. Certainly the short follow-up time might limit this study's significance (or lack thereof). The authors correctly point out that larger studies with longer follow-up and better blinding may be needed in order to determine the ultimate role of this treatment modality in the treatment of OAB. The slight improvement in the one measure may not be enough to make a convert out of very many traditional providers, but the door remains open for patients and/or their providers to walk through.

So why would I include this article in this publication, which is designed to bring you evidence-based science? Because this *IS* evidence-based and it does help us practice. "How?" you might ask. That's a fair question. First, we must acknowledge that the study was well-designed and completed. Second, remember that good science doesn't mean that only positive results are important. A lack of statistical significance helps us advance our practice also, by putting certain treatments in proper perspective. The fact that some benefit was seen in daytime micturition frequency was not a big change in sum, but for an individual patient, there is the possibility that they might be. Similarly, the lack of significant improvement in the other measures in this relatively small study is not very encouraging, but the possibility of benefit has not been eliminated.

So do I recommend this technique? I must admit that I have not; however, the practitioners in this region are limited. I certainly have not dissuaded patients who have asked about other alternative treatments as many of them have not been systematically studied for various maladies. To me, acupuncture is far more "mainstream" these days. Massage therapy is definitely widely used. How far "out there" you want to encourage your patients to seek alternative treatments must be an individualized decision, based on your comfort, the patient's willingness, as well as the specific medical condition. My key word for the day in this regard is to be "open-minded." You may well be surprised. ■

Pharmacology Update

Lanreotide Injection (Somatulin® Depot)

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.

A SECOND SOMATOSTATIN (GROWTH HORMONE inhibiting hormone) analog is available for the

long-term treatment of acromegaly in patients who have not responded to other treatment modalities. Lanreotide is a synthetic cyclical octapeptide, similar to octreotide (Sandostatin) with biological activity similar to naturally occurring somatostatin. The drug was approved with an Orphan designation for treating a rare disease. It is manufactured by Ipsen Biotech in France and marketed by Tercica, Inc as Somatulin Depot.

Indications

Lanreotide is indicated for the long-term treatment of acromegaly in patients who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy.[1]

Dosage

The recommended starting dose is 90 mg given by deep subcutaneous injection (superior external quadrant of the buttock) at 4-week intervals for 3 months. The dose is 60 mg for patients with moderate and severe renal or hepatic impairment. The dose is then adjusted based on growth hormone (GH) and insulin growth factor-1 (IGF-1) levels.[1]

Lanreotide in available as 60 mg, 90 mg, and 120 mg single-use, pre-filled syringes.

Potential Advantages

Lanreotide is premixed and supplied as single use syringes for deep subcutaneous injection while the other available long-acting somatostatin analog, octreotide (Sandostatin LAR Depot), must be administered intragluteally under the supervision of a physician.

Potential Disadvantages

Adverse events are generally related to the pharmacology of lanreotide. These include gall stone formation, and inhibits the release of insulin, glucagon, and thyroid releasing hormone. Most common adverse events include abdominal pain, diarrhea, nausea, bradycardia, hypertension, injection site effects, anemia, and weight decrease. Diabetics may require an adjustment of their diabetes medication. Lanreotide may decrease the bioavailability of cyclosporine.[1]

Comments

Somatostatin analogs (octreotide and lanreotide) act on the somatostatin receptor subtypes 2 and 5 resulting in the inhibition of the release of growth hormone. These analogs have plasma half-lives about 20 times that of native somatostatin. The efficacy of lanreotide was shown in two long-term, randomized studies.[1] In the first study (n = 108), active acromegaly patients with GH > 5 ng/ml were randomized to a single dose 60 mg, 90, 120 mg, placebo. Each patient then entered a fixed-dose phase (16 weeks) followed by dose-titration phase (32 weeks). At 52-weeks or last observation carried forward, the median reduction in GH was 75.5% and median reduction in IGF-1 was 55.4%. Forty-four percent achieved age-adjusted normal IGF-1 and GH ≤ 2.5 ng/ml. Improvement achieved at 16-weeks was maintained for the duration of the study. In the second study (n = 63), patients with IGF-1 concentrations ≥ 1.3 times ULN were administered 90 mg for 4 months followed by dose titration phase up to 48 weeks. At the end of the study the median reduction in IGF-1 was 50.3% with 38% achieving age-adjusted ICF-1 and GH ≤ 2.5 ng/ml. The median GH reduction was 78.6%. In addition to biochemical changes somatostatin analogs shrink pituitary adenomas, improve sleep apnea, reduce left ventricular hypertrophy, improve diastolic function, shorten and normalize QT complex, improve lipid profiles, reduce fatigue and headaches, improve paresthesias, perspiration, osteoarthralgia, carpal tunnel syndrome, and reduce soft tissue enlargement.[2] Studies of lanreotide in patients previously treated with octreotide LAR or crossover studies involving 10 to 23 patients suggest similar efficacy and adverse events between long acting forms of lanreotide and octreotide.[3,4,5] Some patients may be dosed every 6-8 weeks instead of every 4 weeks with out loss of efficacy.[4]

Clinical Implications

Acromegaly is a rare endocrine disorder caused by a growth hormone producing pituitary tumor resulting in over production of GH and ICF-1. It is associated with significant morbidity and reduction in life expectancy of 5 to 10 years.[6] The goal of therapy is to relieve symptoms, restore metabolic changes due to GH excess, and achieve normal physiologic GH levels. First line therapy is surgery or radiotherapy or a combination. Pharmacotherapy includes somatostatin analogs and dopamine agonist.[7] Lanreotide offers another, potentially more patient-friendly somatostatin analog. ■

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CME Questions

15. Choose the incorrect statement.

a. A woman's bra cup size at age 20 is directly related to her risk of developing diabetes mellitus.
b. Women who wore a bra cup size of D or greater developed diabetes mellitus earlier than women who wore an A-cup.
c. Women who wore a bra cup size of D or greater developed breasts later than women who wore an A-cup.
d. Body mass index and bra cup size are independent risk factors for diabetes.

16. In the study by Tanabe and coworkers, those patients without a prior history of hypertension and elevated blood pressure (BP) measurements in the emergency department:

a. Were likely to have pain as the main reason and had no further elevation of BP at home.
b. Were caused by anxiety and had no further elevation at home.
c. Associated with generalized anxiety disorder.
d. Were likely to have persistent BP elevations at home.
e. Directly correlated to the incidence of stage II hypertension.

Answers: 15 (c); 16 (d)

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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.

Clinical Briefs

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

Dr. Kuritzky is a consultant for GlaxoSmithKline and is on the speaker's bureau of GlaxoSmithKline, 3M, Wyeth-Ayerst, Pfizer, Novartis, Bristol-Myers Squibb, AstraZeneca, Jones Pharma, and Boehringer Ingelheim.

Erectile Dysfunction is a CVD Predictor

Erectile dysfunction (ED) most commonly reflects endothelial dysfunction of the corpora cavernosa. Because the risk factors for ED have been determined to be the same as those for cardiovascular disease (CVD), the concept that ED might actually be a predictor for CVD has garnered some support.

The Krimpen Study is a prospective observational study of men (n=3,924) between the ages of 50-75 residing in Krimpen, the Netherlands. From this population, all men aged 50-70 years responded to a question about erectile function. Men who were free of CVD at baseline (n=1,248) were followed for a mean of 6.3 years to compare the rate of CVD events in men reporting ED vs those without. Framingham risk scores were calculated at enrollment. Because this study sought to identify the relationship between ED and CVD, men with incident urologic disorders commonly associated with ED (eg, prostatectomy) were excluded.

After 7,945 person-years of follow up, the hazard ratio for CVD events among men with ED was 1.6 compared to men without ED at baseline. Men with the most severe ED had an even greater risk for CVD (hazard ratio = 2.6). The risk for CVD in this population was independent of Framingham risk score. This study confirms previous observations that ED is a predictor of CVD risk. Clinicians should address the CVD risk profile of men presenting with ED, even in the absence of other manifest vascular disease. ■

Schouten BWV, et al. Int J Impotence Research. 2008;20:92-99.

Does Traditional Thyroid Replacement (Levothyroxine) Adequately Restore T_3?

Most circulating triiodothyronine (T_3) is created by peripheral conversion of levothyroxine (T_4), although the thyroid gland does directly produce 15-20% of plasma T_3. Hypothyroidism is generally treated solely with T_4 replacement, providing sufficient substrate for conversion to T_3 and to consistently restore the euthyroid state as measured by TSH normalization. Previous trials of "dual thyroid replacement" (combinations of T_3 and T_4) have not been convincingly advantageous. With post-thyroidectomy, even though TSH is normalized with levothyroxine monotherapy, the question remains whether T_3 restoration is truly adequate, given that the thyroid gland is no longer present to create its typical 15% of total T_3. One way to assess this is to compare the T_3 levels in subjects pre-and-post thyroidectomy who receive levothyroxine replacement.

Prior to thyroidectomy, 50 euthyroid subjects had measurement of T_3 and T_4. After sufficient levothyroxine replacement to restore euthyroidism (as assessed by TSH < 4.5 mIU/L), serum T_3 and T_4 were compared to pre-surgical levels.

Compared to pre-surgery baseline, levothyroxine replacement resulted in essentially unchanged T_3 levels. However, the T_4 levels attained, while still normal, were 33% higher than pretreatment.

T_3 levels provided by traditional levothyroxine treatment are comparable to those seen in the euthyroid state; the authors reflect that the higher (albeit still therapeutic) T_4 levels seen with levothyroxine replacement may be necessary to ensure adequate T_3. ■

Jonklaas J, et al. JAMA. 2008;299(7):769-777.

Accuracy of Modern Glucose Meters

Both the AAFP and the ADA recommend self-monitoring of blood glucose (SMBG) as an integral component of overall diabetes disease management. Accuracy of SMBG must be assured in order to confidently modulate interventions effectively.

Because capillary blood (eg, fingerstick) glucose is 10-15% lower than venous plasma glucose, most monitors present their results corrected to venous glucose levels. The ADA criteria for accuracy suggest that future systems should provide results within 10% of reference standard within the glucose range of 30-400 mg/dL, although currently available devices are subject to a slightly more tolerant 15% variability.

A metric called the Clarke Error Grid (CEG) segments SMBG results as compared to a reference laboratory into multiple zones: Zone A includes clinically accurate results which should lead to clinically correct treatment; Zone B includes results that deviate by 20% or more from reference standards, but results so-obtained would result in no treatment change or benign treatment changes. Zones C, D, and E are misreadings of sufficient inaccuracy that they could result in meaningfully inappropriate treatment.

Detailed results from 172 patients tested with the OneTouch Ultra 2 show that SMBG results fall within Zone A 99% of the time, and no results were in Zone C, D, or E. Similar findings have been determined for the Ascensia Confirm, the Liberty, the EasyTouch, and OneTouch Ultra.

The authors further explain the most common source of SMBG errors: user error. But clinicians should be reassured that when used properly, currently available SMBG devices are remarkably accurate and unlikely to lead to inappropriate treatment. ■

Bergenstal RM. Insulin. 2008;3:4-14.

A "Run of VT"

By Ken Grauer, MD, *Professor, Department of Community Health and Family Medicine, University of Florida*
Dr. Grauer is the sole proprietor of KG-EKG Press, and publisher of an ECG pocket brain book.

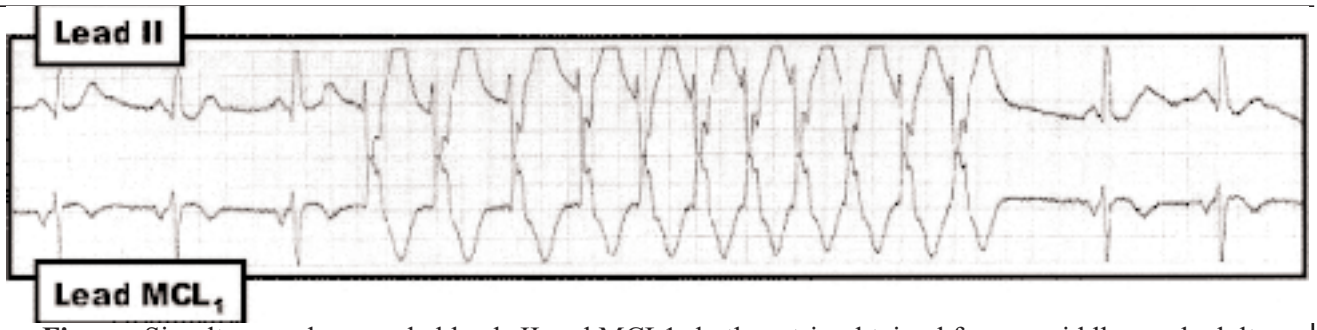

Figure: Simultaneously recorded leads II and MCL1 rhythm strip obtained from a middle-aged adult with heart disease. Despite this "run of VT", the patient remained alert, hemodynamically stable, and asymptomatic during tachycardia.

Clinical Scenario:

Hospital-based physicians (especially those who work night shifts) will often be called about "a run of VT". When not immediately at the patient's bedside, what questions should you ask of the nurse who is caring for the patient? Apply this to assessment of the rhythm above.

Interpretation/Answer:

There are three principle issues to address when assessing a "run of VT (ventricular tachycardia)":

1. How is the patient during the run? Management decisions will vary greatly depending on whether the patient is symptomatic or not, and whether the patient is hemodynamically stable or about to go into cardiac arrest.

2. Is the run "real", and truly VT? What is the ventricular rate *during* the run, and is it sustained? Be sure that the rhythm is not rapidly-occurring artifact that may simulate VT. Realize that relatively *slow* ventricular rhythms (ie, less than 120/minute) represent AIVR (accelerated idioventricular rhythm) rather than true "VT". Hemodynamic compromise is far less likely with AIVR, and such rhythms *rarely* require specific antiarrhythmic treatment.

3. Clinically, *what else* is going on with the patient? A non-sustained ventricular rhythm that does not produce significant symptoms is preferentially treated by correction of underlying predisposing or exacerbating factors. These may include heart failure, ischemia, hypotension from a variety of causes, hypoxemia, acid-base and/or electrolyte disturbance (especially hypokalemia and hypomag-nesemia). Potentially arrhythmia-inducing pharmacologic agents such as sympathomimetics, cocaine, amphetamines, and alcohol should be stopped. The treatment approach will obviously be different for hemodynamically significant VT, in which case antiarrhythmic agents (ie, amiodarone) and/or acute cardioversion are indicated.

Applying these concepts to the rhythm in the Figure, the tracing begins with three beats of normal sinus rhythm. An 11-beat run of NSVT (non-sustained ventricular tachycardia) follows. The run is relatively slow and irregular at first ("*warm-up*" phenomenon), before speeding up to a more regular and rapid rate of 150/minute. This rhythm is clearly VT, as judged by QRS widening with a very different QRS morphology from sinus-conducted beats, lack of premature P wave prior to the onset of the run, and post-ectopic pause following the run. That said, the patient remained alert, asymptomatic and hemodynamically stable during the run—ergo, specific antiarrhythmic treatment was not needed. Instead, correction of hypoxemia and hypomagnesemia controlled the patient's ventricular ectopy and eliminated the runs of VT.

In Future Issues:

Rapid Protection of the Gastroduodenal Mucosa Against Aspirin-Induced Damage by Rabeprazole

PHARMACOLOGY WATCH

Supplement to Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.

Erythropoietin and Cancer Death Rates

In this issue: Does erythropoietin worsen cancer death rates? Most hypothyroid patients can be replaced with levothyroxine alone without additional T3. Does aggressive control in type 2 diabetes save lives?

Erythropoiesis-stimulating agents (ESAs) may increase the risk of death in cancer patients according to a new meta-analysis, which also suggests that the drugs are associated with a significant risk of venous thromboembolism (VTE). Researchers evaluated Phase 3 trials comparing ESAs (erythropoietin and darbepoetin) with placebo or standard care in the treatment of anemia among patients with cancer. The study included 51 trials with 13,611 patients that included survival information, and 38 clinical trials with 8172 patients that included information on VTE. Cancer patients who received ESAs had a higher rate of VTE (7.5% vs 4.9%, RR 1.57 7:95% CI, 1.31-1.87) and increased mortality risks (hazard ratio 1.10: 95% CI, 1.01-1.20). The risk of VTE has been previously reported, but this is the first report that raises the issue of increased mortality associated with use of the drugs. The authors cite eight recent studies which have shown increased rates of tumor progression or mortality with ESA use. These trials raise the concern that the ESAs directly affect tumors, a plausible theory since expression of erythropoietin and erythropoietin receptors has been demonstrated in a variety of human cancers and stimulation of these receptors has been shown to cause tumor effects including proliferation, antiapoptosis, and invasion. The authors conclude that the ESA administration to patients with cancer is associated with increased VTE and mortality risks, and raises concerns about the safety of ESA administration to patients with cancer (*JAMA.* 2008; 299 (8): 914-924). The FDA has indicated that it will hold a meeting of its Oncologic Drug Advisory Committee in March to review the safety concerns.

Thyroid Replacement Debate Continues

Debate has raged for years whether thyroid replacement with levothyroxine (LT4) provides adequate levels of triiodothyronine (T3) through peripheral conversion, or whether LT4 should be routinely supplemented with T3 in hypothyroid patients. Researchers from Georgetown measured preoperative T3 levels in 50 euthyroid patients undergoing total thyroidectomy. These levels were then compared with postoperative levels T3 while receiving replacement therapy with LT4. There were no significant decreases in T3 concentration in patients receiving LT4 therapy compared with their pre-thyroidectomy T3 levels. Free T4 concentrations were significantly higher in patients treated with LT4 therapy compared with their preoperative T4 levels. Serum TSH levels of 4.5 mIU/L or less were achieved in 94% of patients in the study, however T3 concentrations were significantly lower in the group with TSH levels greater than 4.5. The authors conclude that replacement therapy with levothyroxine (LT4) to achieve TSH levels less than 4.5 results in normal T3 levels through peripheral conversion of T4 to T3, suggesting that T3 administration is not necessary (*JAMA.* 2008:299:769-777). In an

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accompanying editorial, David S. Cooper M.D. reminds us that T3 is the active thyroid hormone and has two sources, 20% is produced by the thyroid gland and the other 80% is converted from T4 in peripheral tissues. The peripheral conversion can be affected by starvation, overfeeding, and acute and chronic illness as well as drugs. Multiple studies have shown that replacement with T3 and T4 has no value over replacement with T4 alone. Regardless, many compounding pharmacies continued to prepare long-acting T3 preparations, and such preparations are common in alternative medical practices. Dr. Cooper also notes that several patients in the study cited above did not achieve normal T3 levels with LT4 replacement, and suggests that there is a subset of patients who may benefit from T3 replacement as well. But for the average patient on thyroid replacement this study shows that LT4 replacement alone is adequate (*JAMA*. 2008; 299:817-819).

Type 2 Diabetes Treatment Okay if Not Too Tight

Tight control of type 2 diabetes is beneficial as long as the control is not too tight. This is the rather confusing message of several recent studies. Aggressive multifactorial intervention in type 2 diabetes including tight glucose regulation, use of renin-angiotensin system blockers, aspirin, and lipid-lowering agents significantly improves mortality according to new study from the *New England Journal of Medicine*. Researchers in Denmark randomized 160 patients with type 2 diabetes and persistent microalbuminuria to receive either intensive therapy or conventional therapy for a mean of 7.8 years. Patients were subsequently followed for an additional 5.5 years with conventional therapy patients converted to intensive therapy. The primary endpoint at 13.3 years of follow-up was time to death from any cause. The intensive therapy group followed the latest guidelines from the American Diabetes Association, which included hemoglobin A1c target levels of less than 6.5%, a fasting serum total cholesterol level of less than 175 mg/dl, a fasting serum triglyceride level of less than 150 mg/dl, a systolic blood pressure of less than 130 mm Hg, and diastolic blood pressure of less than 80 mm Hg. Patients were treated with renin-angiotensin blockers (ACEI or ARB), and received low-dose aspirin. After 13.3 years, 40 patients in the conventional therapy group died as compared to 24 in the intensive therapy group (hazard ratio[HR} 0.54; 95% CI 0.32-0.89; *P*= 0.04). Intensive therapy was associate with a lower risk of death from cardiovascular disease (HR 0.43; *P*=0.04) and of all cardiovascular events (HR 0.4; P <0.001). Six patients in the conventional therapy group ended up with end-stage renal disease compared to one in the intensive therapy group (*P*=0.04). Fewer patients in the intensive therapy group required retinal photocoagulation as well. The authors conclude that at-risk patients with type 2 diabetes benefit from intensive intervention with multiple drug combinations and behavior modification, and have a sustained benefit with respect to vascular complications and death rates from cardiovascular causes (*NEJM.* 2008;358:580-591). The study stands in contrast to a recent announcement from the National Heart, Lung, and Blood Institute (NHLBI) that they are halting the aggressive treatment arm of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial because of of a higher mortality rate. The trial enrolled 10,251 at-risk type 2 diabetics who were randomized to medical strategies to intensely lower blood sugar below current recommendations vs less intensive treatment. The aggressive arm targeted hemoglobin A1c levels under 6% while the standard treatment arm had a target between 7% and 7.9%. There were 257 deaths in the intensive treatment group compared with 203 in the standard treatment group over an average of four years of treatment. Extensive analysis has not determined the specific cause for the increased death rate, and no drugs have been specifically implicated including the thiazolidnediones. In Canada, a similar trial (ADVANCE) has enrolled over 11,000 high risk type 2 diabetic patients with a similar design—routine care vs intensive glucose control (A1c <6.5) and risk factor management. ADVANCE researchers have reviewed their data and have found no increase mortality in their aggressive treatment group so far and their study continues.

FDA Actions

The FDA has approved bevacizumab (Avastin) for first-line treatment of women with metastatic HER2-negative breast cancer. When used in combination with paclitaxel, disease progression was reduced by 52% compared to treatment with paclitaxel alone. The approval was done under the FDA's accelerated approval program. Bevacizumab is manufactured by Genentech Inc.

The FDA has issued an early communication about an ongoing safety review of botulinum toxin Type A (Botox) and Type B (Myobloc) regarding reports of systemic adverse reactions including respiratory compromise and death. The reactions are suggestive of botulism. Many of these events occurred in children treated for cerebral palsy-associated limb spasticity, although reports of occurred for other uses in adults as well. The FDA's warning of health care professionals to watch for systemic effects as much as one day after injections including dysphasia, dysphonia, weakness, dyspnea or respiratory distress. ■

Note: *The February 2008 issue of Pharmacology Watch stated that Bystolic was marketed by Mylan Bertek. It should be noted that Bystolic is marketed by Forest Laboratories as well.*