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Color Me Purple

ABSTRACT & COMMENTARY

Synopsis: *Ingesting moderate amounts of purple GJ each day appeared to improve endothelial function as measured by FMD in patients with known arteriosclerotic coronary arterial disease.*

Source: Chou EJ, et al. *Am J Cardiol.* 2001;88:553-555.

Flavonoids are known to be powerful antioxidants that improve endothelial function and inhibit platelet aggregation[1-3] thereby presumably slowing or preventing coronary atherosclerosis and decreasing the frequency of acute coronary syndromes. For more than 20 years, cardiologists and epidemiologists have suggested that the "French paradox" (ie, the fact that the coronary heart disease mortality rate in France is lower than it is in other industrialized nations with similar prevalences of coronary risk factors) is due to the ingestion of the flavonoids[4,5] found in red wine and purple grape juice (GJ).

Dr. Eric Chou and his associates from the University of Wisconsin Medical School used an unrestricted grant from Welch's Foods, Inc. to perform a study on the effect of 2 different doses of purple GJ alone and in combination with vitamin E on endothelial function. One group of 11 subjects consumed 21 ounces of concord GJ daily for 56 days and a second consumed approximately 10½ ounces daily for the same period of time. After 28 days all subjects were given 400 international units of vitamin E daily. Endothelial function was assessed by measuring flow-mediated vasodilatation (FMD) of the brachial artery using B-mode ultrasound. Resting brachial artery diameters and blood flow scans were obtained before and after the administration of sublingual nitroglycerin. FMD was calculated as a ratio of the brachial artery diameter after reactive hyperemia compared to the baseline diameter, expressed as a percent change. FMD of the brachial artery was improved after ingestion of GJ and it appeared that the degree of improvement was the same regardless of whether high or low doses of GJ were ingested. Furthermore, the results revealed that adding a vitamin E supplement to the purple GJ did not further improve endothelial function.

COMMENT BY HAROLD L. KARPMAN, MD, FACC, FACP

The "French paradox" observation has largely been attributed to

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INSIDE

the regular consumption of modest amounts of alcohol-containing beverages that were presumed to increase high density lipoprotein (HDL) cholesterol levels and inhibit platelet function.[4-10] Several studies have suggested that red wine, which contains several hundred different types of flavonoids, was more cardioprotective than the alcohol-containing beverages such as beer or spirits[4-7] and other studies have concluded that the observed positive effects were due to the flavonoids present in red wine and GJ.

Chou et al's study is open to many criticisms because the sample size was extremely small, the time frame of the study was relatively short, and the brachial artery technique for evaluating endothelial function, although sensitive and reproducible, may not accurately reflect all aspects of endothelial function since it is only a simple objective measurement of FMD. Despite these shortcomings, the findings do confirm the results of other studies which suggest that pharmaceutical agents and/or natural food substances may be capable of altering endothelial function in a positive way. The validity of the results were also somewhat enhanced by the fact that each subject's baseline brachial artery reactivity (ie, FMD) served as a control value and was compared with the results obtained in the same individual after GJ ingestion.

In summary, ingesting moderate amounts of purple GJ each day appeared to improve endothelial function as measured by FMD in patients with known arteriosclerotic coronary arterial disease. Despite the high-glucose content (ie, 56-112 g of carbohydrate) in the ingested GJ, adverse effects on lipid and glucose metabolism did not occur. If the results of this study can be reduplicated in larger groups of patients and especially, if outcome studies demonstrate a decrease in cardiovascular events as a result of ingesting GJ, the time may come when physicians will be recommending the daily ingestion of GJ alone or possibly even in combination with moderate amounts of alcoholic beverages. ❖

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Midlife Vascular Risk Factors and Late-Life Mild Cognitive Impairment

ABSTRACT & COMMENTARY

Synopsis: *This study found a dose-response relationship between elevated cholesterol and SBP at midlife and severity of cognitive decline in late life.*

Source: Kivipelto M, et al. *Neurology.* 2001;56:1683-1689.

Age-related cognitive decline or mild cognitive impairment (MCI) has attracted medical attention because of its relationship to Alzheimer's disease (AD). Petersen and associates noted an annual conversion to AD in 10-12% of MCI subjects compared to a conversion rate

of only 1-2% in the normal elderly population.[1] There also is evidence that a relationship exists between hypertension and hypercholesterolemia and late-life cognitive decline.[2-4]

Kivipelto and colleagues evaluated the effect of midlife elevated serum cholesterol levels and blood pressure on the subsequent development of MCI in a Finnish population. Subjects were derived from random population-based samples from surveys carried out from 1972 to 1987. After an average follow-up of 21 years, more than 1400 subjects aged 65-79 were re-examined in 1998. Subjects scoring £ 24 on the MMSE (n = 280) were invited to participate in further testing that included thorough medical and neurological examinations and detailed neuropsychological evaluation. MCI was diagnosed according to criteria devised by the Mayo Clinic Alzheimer Disease Research Center.[5] By applying these criteria the prevalence of MCI in this population was 6.1% (n = 82), after excluding subjects with other health problems that may have had a direct impact on cognitive, the prevalence was 4.8% (n = 64). In these subjects, a high serum cholesterol level (‡6.5 mmol/L) at midlife was a significant risk factor for MCI (odds ratio 1.9; 95%; CI, 1.2-3.0). Subjects with MCI tended to have higher systolic blood pressure (SBP) at midlife than controls, and the distribution of SBP values was wider among MCI than control subjects. High midlife SBP approached, but did not reach, significance as a risk for MCI. Sixty-one percent of subjects with MCI had either elevated serum cholesterol or high SBP at midlife. There was no significant difference in the prevalence of cardiovascular or cerebrovascular disease between MCI and control subjects.

Kivipelto et al found a dose-response relationship between elevated cholesterol and SBP at midlife and severity of cognitive decline in late life. At midlife, subjects with MCI had cholesterol and SBP levels that were higher than those of control subjects but lower than those who developed dementia. This graded association may indicate a causal relationship between midlife hypercholesterolemia and systolic hypertension and the severity of late-life cognitive impairment.

COMMENT BY JOHN J. CARONNA, MD

As the proportion of the elderly increases in the population, so must the number of patients with AD. In the absence of a cure for the condition, any interventions that might delay its onset would have huge public health benefits.

Kivipelto et al have highlighted the relationship between vascular factors, especially hypercholesterolemia and cognitive impairment. These factors may simply increase the risk of dementia by inducing cerebrovascular atherosclerosis and impairing cerebral blood flow. Recently, however, the possible biologic mechanisms whereby elevated serum cholesterol could cause cognitive decline have been studied. Cholesterol modulates the metabolism of amyloid precursor protein in cell cultures,[6] and depletion of intraneuronal cholesterol inhibits the production of ß-amyloid in vitro.[7] Therefore, it is possible in patients with hypercholesterolemia that increased levels of CNS cholesterol could accelerate the accumulation of ß-amyloid plaques and the development of AD. If this is so, then the benefits of treatment of hypercholesterolemia with statins may be more far-reaching and important than previously appreciated. ❖

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Fatal Pseudomembranous Colitis Associated with a Variant *C difficile* Strain

ABSTRACT & COMMENTARY

Synopsis: *Antibiotics may lead to severe/fatal pseudomembranous colitis despite negative tests for toxin and "negative" cultures.*

Source: Johnson S, et al. *Ann Intern Med*. 2001;135:434-438.

An 86-year-old man with multiple cardiopulmonary problems was admitted to a tertiary hospital for apparent inflammatory bowel disease with refractory diarrhea, fever, and leucocytosis. His stool had been tested for *Clostridium difficile* toxin with negative results, but culture was positive for *C difficile*. However, the isolate was tested as negative for toxin. Although colonoscopy findings were suspicious for antibiotic colitis, the diagnosis was dismissed due to 2 additional stool specimens that tested negative for toxin A despite the

presence of an apparent nontoxigenic strain of *C difficile*. Steroid treatment was started for suspected IBD, but the patient died of cardiopulmonary arrest. Later postmortem studies revealed that a toxin variant was produced by the *C difficile* strain, but this was not recognized by the clinically available toxin test. In a telephone survey, Johnson and colleagues found that 46% of queried hospital laboratories used only the immunoassay for toxin A to detect *C difficile* (similar results found in a study in the United Kingdom in 243 laboratories).

COMMENT BY MALCOLM ROBINSON, MD, FACP, FACG

Had the stool specimens been tested with an in vivo cytotoxin test, the correct diagnosis would have been made. In hospitals where such testing is not available, it is critically important to remember that *C difficile*-induced diarrhea may be present in patients despite negative standard test results for *C difficile* toxin. ❖

Is it TIME For a Change of Heart?

ABSTRACT & COMMENTARY

Synopsis: *The TIME trial found that invasive vs. medical therapy in elderly patients with symptomatic coronary disease resulted in a higher quality of life in patients older than 75.*

Source: The TIME Investigators. *Lancet.* 2001;358:951-957.

The time trial randomized 305 elderly patients (age > 75) with angina refractory to medical management to receive either aggressive medical management or invasive management. Patients who had experienced a myocardial infarction or predominant congestive heart failure in the past 10 days were excluded, as were patients who had life-limiting diagnoses. All patients had experienced angina despite at least 2 anti-anginal drugs. The primary end point was a quality-of- life survey that was completed before randomization and 6 months later. Secondary end points included an index of major adverse cardiac events.

Twenty-six percent of the patients assigned to the invasive strategy were not candidates for angioplasty or surgery and were treated with medical management. Thirty-six percent of the medical management group required invasive therapy within 6 months. Data were interpreted with an intention-to-treat analysis. Nineteen percent of patients did not complete the quality-of-life questionnaire at the study's conclusion.

Quality of life was higher in the invasive group. The mean improvement on the SF36 general health survey was 7 points (95% CI, 2-13; $P = 0.001$); the mean improvement on the SF36 vitality index was 5 points (95% CI, -2-11; $P = 0.001$).

Forty-nine percent of patients assigned to the medical management group had a major adverse cardiac event; 19% of the invasive management group had an event. This was predominantly due to a reduction in readmissions to the hospital (10% in the invasive group vs 50% in the medial management group). The mortality rate was higher in the subjects assigned to the invasive group (8% vs 4%; $P = 0.15$).

COMMENT BY JEFF WIESE, MD

Two previous trials have established that invasive management of refractory angina is superior to medical management in improving quality of life.[1,2] This trial asks the important question of whether this finding applies to patients older than 75 years of age.

The validity of this trial was compromised by the small number of subjects and ineffective randomization. More patients in the invasive management group were receiving beta blockers (82% vs 72%); more patients in the medical management group were receiving ACE inhibitors (35% vs 23%). Validity was further compromised by the high degree of crossover between the 2 groups, and the number of patients (19%) who did not complete the quality-of-life questionnaire.

Generalizing this study to clinical practice may be limited. Forty percent of the medical management group were already receiving 3 or more antianginal drugs. The expected benefit of aggressive medical management may have been limited; many patients appear to have been maximally medically managed at the onset of the trial. Fifty-five percent of patients had the dose of their current medications increased; the average increase in medications was 0.8. In this way, the medical management group served more as a control than as an alternative treatment strategy.

The trial nonetheless provides insight into the potential costs and benefits of invasive management in the elderly. Invasive management improved quality of life and readmission rate. Three patients would have to be treated with invasive therapy to prevent 1 readmission to the hospital. This benefit came at a cost, however, there was a nonstatistically significant increase in mortality in the invasive group. The number needed to harm was 25.

The TIME investigators note that a larger clinical trial is ongoing. This will be required to provide reliable insight into the potential costs and benefits of invasive

vs. medical management. For now, this trial suggests that both aggressive medical management and invasive therapy can improve quality of life in patients older than 75. Invasive medical management should be considered for patients who value an improved quality of life over the potential risk of mortality from the procedure. ❖

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Pharmacology Update

Darbepoetin Alfa—A New Treatment for Anemia Associated with CRF

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

Darbepoetin alfa, a new recombinant erythropoietic protein recently approved by the FDA for the treatment of anemia associated with chronic renal failure (CRF). Darbepoetin, known as novel erythropoiesis stimulating protein, has a longer serum half-life than epoetin alfa which allows for less frequent dosing. The new drug is a hyperglycosylated analog of recombinant human erythropoietin (epoetin alfa) produced by recombinant DNA technology using Chinese hamster ovary cells. Amgen markets it under the trade name Aranesp.

Indication

Darbepoetin is indicated for the treatment of anemia associated with CRF. It is indicated for both predialysis and dialysis patients.[1]

Dosage

The recommended starting dose for correcting anemia is 0.45 µg/kg given as a single intravenous or subcutaneous dose once weekly. The dose should be adjusted to achieve and maintain target hemoglobin not to exceed 12 g/dL. Dose adjustments should not be made more frequently than once monthly. If hemoglobin is increasing and approaching 12 mg/dL, the dose should be reduced by about 25%. If hemoglobin continues to increase, the dose should be temporarily withheld until the level begins to decrease. The dose of darbepoetin alfa should then be reinstated at 25% of the previous dose. If hemoglobin increases > 1.0 g/dL in a 2-week period the dose should also be reduced by 25%.[1]

In many patients, particularly those in predialysis, maintenance dose may be lower than the starting dose.

Epoetin alfa may be converted to darbepoetin alfa based on the weekly dose of epoetin alfa.[1] The estimated starting dose for darbepoetin alfa is 6.25 µg for patients on < 2500 units of epoetin alfa weekly; 12.5 µg for 2500-4999; 25 µg for 5000-10,999; 40 µg for 11,000-17,999; 60 µg for 18,000-33,999; 100 µg for 34,000-89,999; and 200 µg for 90,000 or greater. Patients previously receiving epoetin alfa 2-3 times a week should be administered darbepoetin alfa once weekly. Those receiving epoetin alfa once weekly should be administered darbepoetin alfa every 2 weeks.

Darbepoetin alfa is supplied as 25 µg, 45 µg, 60 µg, 100 µg, and 200 µg/mL in single 1 mL vials. The vials should not be shaken, diluted, or mixed with other drug solutions.[1]

Potential Advantages

Darbepoetin alfa has an elimination half-life about 3-fold longer than epoetin alfa (25.3 h vs 8.5 h) which permits less frequent dosing.[2] Darbepoetin alfa can be dosed once weekly or once every other week compared to epoetin alfa, which is generally dosed from 1 to 3 times a week.

Potential Disadvantages

Darbepoetin alfa is only FDA approved for use in CRF and not as adjunct to chemotherapy or other types of anemia. There is a theoretical potential for the formation of neutralizing antibodies, however, the incidence of antibody development has not been adequately studied.[1]

Comments

Darbepoetin alfa was developed by increasing the carbohydrate content of epoetin alfa. The resulting molecule has a 52% carbohydrate content compared to 40% for epoetin alfa and a lower isoelectric point. The 2 drugs have the same mechanism of action. By binding to the erythropoietin receptor on erythroid progenitor cells, they stimulate the proliferation and differentiation of erythrocytes.[3] Darbepoetin's activity in terms of anemia correction in CRF patients is comparable to that of recombinant erythropoietin (epoetin alfa) in previously untreated patients as well as those previously maintained on recombinant epoetin alfa.[3,4] Side effects also appear to be comparable between the 2 drugs.

Darbepoetin alfa is priced roughly comparable to that of epoetin alfa. Darbepoetin is about $4 per µg compared to about $1.10 per 100 unit for epoetin alfa. Depending on the equivalent dose used, darbepoetin alfa may be less expensive or more expensive than epoetin alfa. For example, 2500 units twice a week of epoetin

alfa costs $225 per month. The corresponding dose of darbepoetin alfa, 25 µg once weekly, is priced at $400. However, 25,000 units 3 times a week of epoetin alfa would cost $3300 per month, while the corresponding dose of darbepoetin alfa is $1600 (100 µg weekly). A 5000 unit of epoetin once weekly at the cost of $220 per month would be similar to $200 per month for darbepoetin alfa (25 µg every 2 weeks). These are estimated starting doses and the maintenance doses may differ.

Clinical Implications

Darbepoetin alfa provides a formulation with comparable efficacy and side effects but less frequent dosing compared to epoetin alfa. This may be especially beneficial to patients not currently on dialysis. Amgen has studied darbepoetin alfa as adjunct to chemotherapy and has filed for a supplemental licensing for this indication. ❖

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CME Questions

34. The annual conversion rate of patients with MCI to AD is approximately:

a. 1%.
b. 2%.
c. 5%.
d. 10%.
e. 25%.

35. Antibiotic colitis can be reliably detected by which of the following tests?

a. Use of the immunoassay for toxin A
b. Colonoscopy with biopsies throughout the colon
c. Overall clinical assessment, sometimes requiring use of in vivo cytotoxicity assays in addition to measurement of toxin A
d. Use of both immunoassays for toxin A and toxin B
e. Culture of stool with isolation of *C difficile* species

36. Which of the following is true for a 71-year-old man with angina refractory to medical management?

a. Invasive management (angioplasty or bypass surgery) offers a 6-month mortality benefit over that of aggressive medical management.
b. There is no improvement in quality of life with aggressive medical management.
c. Invasive management offers a superior quality of life when compared to medical management, but it may increase the risk of death.
d. Invasive management improves quality of life, but not in patients older than 70 years of age.

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By Louis Kuritzky, MD

Peripheral Arterial Disease Detection, Awareness, and Treatment in Primary Care

Peripheral arterial disease (PAD) causes substantial morbidity, and is associated with significant mortality, particularly referable to cardiovascular events. Compared to other vasculopathies like stroke and myocardial infarction (MI), which are associated with high levels of public awareness and commonplace incorporation of risk factor reduction on the part of the clinical community, PAD is relatively neglected. The PARTNERS program evaluated detection of PAD in the office setting, hypothesizing that PAD is underdiagnosed and undertreated in primary care.

Patients (n = 6979) from 350 primary care sites older than age 70 (> age 50, if a smoker or diabetic) were screened for PAD using a Doppler device to obtain the ankle-brachial index (ankle systolic blood pressure divided by brachial systolic blood pressure). Since ankle blood pressure should be equal to or greater than brachial, an ABI less than 0.9 is indicative of clinically relevant PAD.

PAD was found in 29% of study subjects, of which the majority had not been previously diagnosed. Less than 10% of PAD subjects were symptomatic. Only half of physicians were aware of the PAD diagnosis in persons previously diagnosed.

Attending to cardiovascular risk factor analysis, Hirsch and colleagues note that smoking cessation had been applied to only half of PAD subjects, and management of both hypertension and hyperlipidemia were less intensive than in comparable patients with cardiovascular disease. PAD, a harbinger of other cardiovascular mortal and morbid end points, has been demonstrated to be underdiagnosed and less intensively managed than other comparable vasculopathies. ❖

Hirsch AT, et al. JAMA. 2001;286: 1317-1324.

Widespread Distribution of UTIs Caused by a Multidrug-Resistant *E coli* Clonal Group

The majority of american women will experience a urinary tract infection (UTI) in their lifetime, and as many as 11% of women report at least 1 UTI per year. Although most *Escherichia coli* strains involved in UTI are susceptible to trimethroprim-sulfamethoxazole, currently more than 15% of isolates are resistant. Since certain clonal strains of *E coli* have caused outbreaks of cystitis and pyleonephritis in Europe, the question has been raised whether there is a specific clone of *E coli* in the United States that has been etiologic in TMP-SMX-resistant UTI.

Study subjects were obtained from a population of California women with symptoms of UTI who cultured positive for *E coli* resistant to TMP-SMX over a 14-week period beginning October 1999; the results were compared with analyses of *E coli* from women with UTI in Michigan and Minnesota.

Considering isolates from all 3 states, 38-50% TMP-SMX resistant *E coli* belonged to a single clonal group. The method of spread of this clonal group is unknown, but the suggestion has been made that contaminated food could harbor such strains. ❖

Manges AR, et al. N Engl J Med. 2001;345:1007-1013.

Selective Postoperative Inhibition of GI Opioid Receptors

Major abdominal surgery consistently produces some degree of ileus, which not only may cause pain, nausea, and vomiting, but also delays return to oral feeding. Ultimately, ileus prolongs hospitalization. The common causes of ileus include the mechanical effects of surgical bowel manipulation, and opioids used in pain management. Opioid analgesia results in anticholinergically derived reductions in bowel motility.

ADL 8-2698 (ADL) is an investigational agent that blocks the gastrointestinal effects of opioid analgesics; because it is poorly absorbed when administered orally, and does not cross the blood-brain, coadministration with opioid analgesics is possible without blockade of opioid-induced centrally-mediated analgesia. The current study included 78 patients who underwent significant abdominal surgery. Patients were randomly assigned to ADL or placebo, both administered orally twice daily.

Participants who received ADL enjoyed shorter time to first passage of flatus (49 vs 70 hours), earlier first bowel movement (70 vs 111 hours), and earlier discharge from the hospital (68 vs 91 hrs). No serious adverse events were reported; indeed, ADL was associated with reduced nausea and vomiting. ADL offers promise as a tool to circumvent anticholinergic effects of postoperative opioid analgesia. ❖

Taguchi A, et al. N Engl J Med. 2001; 345:935-940.

In Future Issues:

Pharmacologic Calvinism: Why Drugs Should Be Used for Indications, Not Side Effects

An Athletic ECG

By Ken Grauer, MD

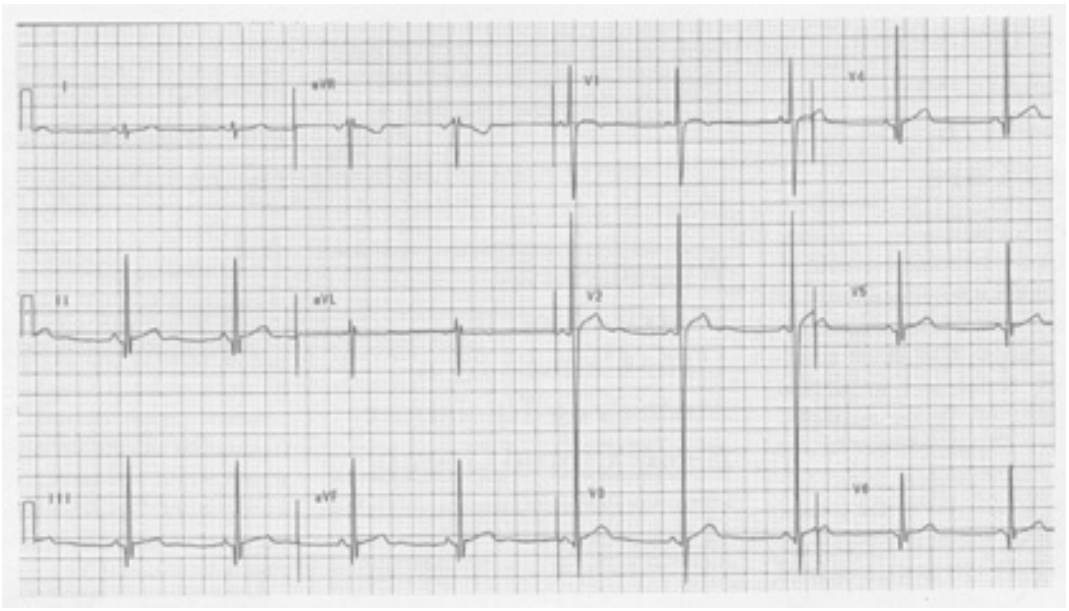

Figure. A 12-lead ECG obtained from a 21-year-old athlete.

Clinical Scenario: The 12-lead ECG shown in the Figure was obtained from a 21-year-old endurance-sport male athlete. What important cardiac abnormality might be present? What else might this ECG be reflective of?

Interpretation: The ECG in the Figure is *not* a normal tracing. There is sinus bradycardia and arrhythmia, normal intervals (PR, QRS, and QT), and a vertical though still normal mean QRS axis of approximately +90°. The findings of concern are several: 1) moderately deep (though narrow) Q waves in multiple leads (II, III, aVF, V_3-V_6); 2) markedly increased QRS amplitude (deep S waves in leads V_1-V_2, and early transition with tall R waves in leads V_2-V_4); and 3) the suggestion of prominent septal forces (tall R wave = S in lead V_1, early transition, and the inferolateral Q waves just noted). In addition, there are some ST-T wave changes consistent with an early repolarization pattern (slight J point ST segment elevation in the inferolateral leads, and ST segment coving in leads V_1-V_4).

ECG abnormalities are commonly seen in otherwise healthy young adults. This is especially true in athletes. A recent study by Pelliccia and colleagues is particularly insightful with regard to the incidence of ECG abnormalities in young adult athletes and the clinical relevance of the abnormalities found (Pelliccia A, et al. *Circulation.* 2000; 102:278-284). Among a series of more than 1000 consecutive young Italian men and women participating in 38 different sporting activities, 60% had a normal or near normal tracing (early repolarization, 1° AV block and incomplete right bundle branch block were *all* considered *near* normal and acceptable normal variants in these otherwise healthy young adult athletes). Forty percent of the overall group had at least mild-to-moderate ECG abnormalities, of which approximately one third had distinctly abnormal tracings. Marked abnormalities were significantly more common in male athletes, athletes younger than 20 years of age, and in those participating in endurance sports (rowing, cycling, cross-country skiing, or long-distance running). Surprisingly, despite even striking ECG abnormalities, structural abnormality (beyond modest physiologic increase in selected cardiac dimensions on echocardiography) was uncommon. The "good" news derived from this study is that the ECG finding of a normal ECG in a young competitive athlete is highly predictive of a normal heart. The problematic result is that as many as 15% of young adult athletes (especially those involved in endurance sports) may have a markedly abnormal ECG, such as the one shown in the Figure. While echocardiography is appropriate (to rule out hypertrophic cardiomyopathy) in individuals such as the 21-year-old athlete in this case, the overwhelming majority of young competitive athletes with distinctly "abnormal" ECGs will end up having a structurally normal heart. ❖

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