COMMENTS AND RESPONSES

Low-Carbohydrate Diets

TO THE EDITOR: Although purporting to show that a low-carbohydrate "Atkins" diet is more beneficial than a conventional "low-fat" American Heart Association/National Cholesterol Education Program (AHA/NCEP) diet, the studies by Yancy and co-workers (1, 2) showed that neither diet effectively decreases weight or levels of low-density lipoprotein (LDL) cholesterol. In both studies, LDL cholesterol levels did not change significantly and there were no significant differences in weight after 1 year (only about 3% weight loss). Similar findings were also seen in an earlier study (3).

The conventional AHA/NCEP “low-fat” diet is not very low in fat or cholesterol and reduces LDL cholesterol levels by only 5% in most patients, if at all (4). Since this diet is often high in refined carbohydrates (which increase triglyceride levels), low-carbohydrate diets often show greater reductions in triglyceride levels, especially when patients take fish oil. In contrast, a 10%-fat, whole-foods diet low in saturated fat and refined carbohydrates and high in complex carbohydrates decreased LDL cholesterol levels by an average of 40% after 1 year in patients not taking lipid-lowering drugs (5). Also, patients lost 24 pounds during the first year and had kept off more than half of that weight 5 years later while controls following an AHA/NCEP diet did not lose weight. Exercise levels between the groups were not significantly different.

Risk factors such as lipids and lipoproteins must be distinguished from direct measures of disease. Studies using serial coronary arteriography to assess patients consuming an AHA/NCEP diet showed that coronary atherosclerosis worsened in most (4). In contrast, patients who followed an unrefined foods diet with only 10% fat (mostly fruits, vegetables, whole grains, and legumes) had significant regression of coronary atherosclerosis after 1 year on quantitative coronary arteriography and even more regression after 5 years (5). In addition, they had 2.5 times fewer cardiac events than controls following an AHA/NCEP diet, who showed more progression of atherosclerosis after 5 years than after 1 year. There was a direct correlation between intake of dietary cholesterol and total fat and changes in coronary atherosclerosis. Others have found similar results (7). Also, 99% of experimental group patients stopped or reversed the progression of coronary heart disease, as measured by cardiac positron emission tomography scans (8).

Only 1 peer-reviewed study examined the effects of the Atkins diet on cardiovascular disease. Myocardial perfusion improvement on a very low-fat whole foods diet but worsened on the Atkins diet (9). Advocates of a low-carbohydrate diet must prove its efficacy in randomized, controlled trials using direct measures of cardiovascular disease, not just risk factors or epidemiologic studies, especially since diets high in saturated fat and red meat are linked to heart disease, cancer, osteoporosis, and renal disease.

The harmful effects of a high-fat diet may be mediated through other mechanisms besides traditional risk factors. For example, dietary fat intake increases plasma levels of factor VII coagulant activity (4). Indeed, 1 man in the low-carbohydrate group in Yancy and colleagues’ study (1) developed angina and coronary artery disease near the end of the study even though his risk factors had improved, and a patient in Stern and colleagues’ study died of ischemic cardiomyopathy (2).

We need to move beyond the simplistic notion that whatever raises high-density lipoprotein (HDL) cholesterol levels is beneficial and anything that lowers them is harmful. High-density lipoprotein cholesterol levels may decrease in patients who reduce dietary fat and cholesterol intake because their need for HDL cholesterol is not as great—in simple terms, when you have less garbage, you need fewer garbagemen. No data prove that physiologic reduction of HDL cholesterol levels with a low-fat diet is detrimental (10).

The debate should not focus only on low carbohydrate versus low fat. Patients have a spectrum of dietary choices. To the degree that they reduce their intake of refined carbohydrates and excessive fats and increase their intake of unrefined carbohydrates (fruits, vegetables, whole grains, legumes) and sufficient ω-3 fatty acids, they may feel better, lose weight, and gain health.

Dean Ornish, MD
University of California, San Francisco, and Preventive Medicine Research Institute Sausalito, CA 94965

References

IN RESPONSE: We share Dr. Ornish’s concerns that neither the conventional low-fat diet nor the low-carbohydrate diet in our study reduced total or LDL cholesterol levels. The scientific evidence that aggressive LDL cholesterol lowering reduces atherosclerosis and ischemic coronary events is strong, although complicated by concomitant beneficial effects on inflammatory markers such as C-reactive protein. The evolving data regarding the long-term benefits of in-
Increasing HDL cholesterol levels and lowering triglyceride levels, at least by pharmacologic means, are also promising with regard to impact on coronary heart disease (1). Moreover, abnormal levels of HDL cholesterol and triglycerides are core features of the metabolic syndrome, which has been strongly associated with atherosclerosis (2). Nevertheless, we agree that extrapolation of these findings to dietary effects on HDL cholesterol may be complicated by unknown effects on reverse cholesterol transport.

The referenced study of patients following an extremely low-fat diet (3) provided important preliminary findings regarding favorable effects of this diet on LDL cholesterol levels and coronary artery disease. However, this study was also limited by its small size (40 patients) and by uncontrolled confounding variables, such as limiting counseling on exercise, smoking cessation, and stress management to the experimental group. The experimental group also lost more weight. In contrast, a much larger study of 423 patients following a Mediterranean diet that did not severely restrict fat decreased long-term cardiovascular event rates (4). In truth, we still do not know the ideal dietary composition to prevent cardiovascular disease and increase weight loss. A focus on fat restriction that results in excess refined carbohydrate intake would be expected to exacerbate features of the metabolic syndrome and thus may increase cardiovascular risk. We hope the available studies show that the ideal goals of dietary modification should be to reduce LDL cholesterol levels and improve features of the metabolic syndrome. A diet that helps attain either of these goals merits further investigation to determine its impact on long-term cardiovascular outcomes.

We also want to clarify that the patient in our study with an ischemic cardiomyopathy already had this condition before enrollment, as stated in the manuscript.

Frederick F. Samaha, MD
Linda Stern, MD
Philadelphia Veterans Affairs Medical Center
Philadelphia, PA 19104

References

Rosiglitazone for Treatment of HIV Lipodystrophy

TO THE EDITOR: I disagree with Hadigan and colleagues (1) that rosiglitazone had positive effects on metabolic indices in HIV lipodystrophy in their study. In fact, mean plasma levels of total and low-density lipoprotein (LDL) cholesterol increased significantly, approximately 13%, with 4 mg of rosiglitazone per day. Surprisingly, Hadigan and colleagues (1) did not comment on the important study by Carr and associates (2) that evaluated rosiglitazone for the same objective. However, compared with Hadigan and colleagues’ study (1), the trial by Carr and associates (2) was larger (108 patients) and longer-term (48 weeks) and used maximum rosiglitazone dosages (4 mg twice daily). Carr and associates (2) also reported significant increases in total and LDL cholesterol levels in the rosiglitazone group. Moreover, plasma triglyceride levels increased significantly in Carr and associates’ study but not in the study by Hadigan and colleagues (1), probably because the latter used submaximal doses of rosiglitazone. Clearly, deterioration of the lipid profile during rosiglitazone therapy can increase the cardiovascular risk of HIV-infected patients, who may already be at high risk mainly because of adverse metabolic effects of antiretroviral therapy (3).

Unlike Hadigan and colleagues (1), Carr and associates (2) found no beneficial effects of rosiglitazone on lipatrophy. The improvement of lipatrophy noted by Hadigan and colleagues (1) could be attributed, at least in part, to the fact that lipatrophy was significantly milder in the rosiglitazone group than in the placebo group at baseline. Chance may also be a factor given the small number of patients. Taken together, the previous data indicate that rosiglitazone can worsen lipid variables in HIV lipodystrophy without clear beneficial effects on fat redistribution. Accordingly, rosiglitazone should be used with caution, if at all, in HIV-infected patients receiving antiretroviral therapy and should be accompanied by close monitoring of the lipid profile.

Nasser Mikhail, MD, MSc
Olive View–UCLA Medical Center
Sylmar, CA 91342

References

IN RESPONSE: We acknowledge that rosiglitazone was associated with modest but statistically significant increases in total cholesterol and LDL cholesterol levels in our study, similar to findings seen in the non-HIV diabetes literature regarding the use of this agent. It is important to recognize, however, that insulin resistance, elevated free fatty acid levels, and hypoadiponectinemia are also significant independent predictors of cardiovascular disease; all of these improved with rosiglitazone therapy in our study sample. Furthermore, evidence shows that peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists increase LDL particle size and increase small high-density lipoprotein particles, thereby creating a less atherogenic lipid profile (1). In addition, PPAR-γ agonists such as pioglitazone may have more favorable effects on lipid levels while improving insulin sensitivity and adipogenesis. We agree that the long-term car-
diovacular effects of thiazolidinediones are not known for this popu-
lation and warrant further investigation.

In contrast to our study, the report by Carr and associates (2) did not demonstrate significant increases in subcutaneous fat after 48 weeks of rosiglitazone therapy compared with placebo in HIV-infected patients with lipoatrophy. There are several important differences between our study and theirs. Hyperinsulinaemia, a surrogate marker for insulin resistance, was required in our study and in the study by Gelato and coworkers (3), which also showed increased subcutaneous fat in response to rosiglitazone. The observed increase in subcutaneous fat in our study is consistent with known biological effects of PPAR-γ agonists in stimulating adipogenesis. Carr and associates (2) showed a 5% mean increase in limb fat with rosiglitazone but a 7% increase with placebo. In contrast, in our study, subcutaneous fat decreased over time in the placebo group but increased in response to rosiglitazone. In Carr and associates’ study, negative findings on limb fat may have been related to the spontaneous improvement in limb fat seen in the placebo group. Furthermore, in their study, use of stavudine, a medication associated with progression of lipoatrophy (4), was disproportionate in the rosiglitazone and placebo groups (53% vs. 26%, respectively). In addition to having less severe lipoatrophy, 25% of the patients in our study were women, compared with only 2% in the study by Carr and associates (2). This may also contribute to differences in study results. Although further study is needed, our data indicate a net potential benefit in metabolic variables and body composition in HIV-infected patients with insulin resistance.

Colleen Hadigan, MD, MPH
Steven Grinspoon, MD
Massachusetts General Hospital
Boston, MA 02114

References

Residents’ Work Hours

TO THE EDITOR: Regarding the articles on residents’ work hours (1–4), I would like to offer my perspective. As a teaching attending physician in a program that implemented the Accreditation Council for Graduate Medical Education (ACGME) recommendations on hours and census in 1997, I lived the most vilifying experience of my professional life. I held teaching sessions in and after rounds despite a 70-hour-per-week job; was unpaid for my overtime; and found on the other side a rapidly spreading “blue-collar mentality” focused on counting patients and hours and on “getting out of here,” certainly not the attitude proper to future professionals. It was a disaster for continuity of care, with patients being handed over to 3 teams in 24 hours because maximum census had been reached.

Even more relevant, if the graduate medical education system in the United States goes forward with the planned guidelines, we must be ready to accept the consequences. Residency time will lengthen. Currently, well-prepared interns can graduate in 3 years in the United States compared with 5 or 6 years in Europe, thanks only to long hours and intense case exposure. Graduates of the new system will probably be unfit to assume the responsibilities, stress, and multitasking of an attending physician, who has no limits on hours, census, and length of shift. Therefore, it will be necessary to make changes similar to those made in Europe, such as implementing a more humane job description for attending physicians by regulating hours for the whole profession (which will lead to doubling of staff and skyrocketing medical care costs) or implementing a hierarchical system in which physicians out of residency, who lack intense hands-on experience, report to a senior physician for major decisions for at least 10 years. This would kill the spirit of professional independence and individual responsibility that U.S. doctors enjoy compared with their continental Europe colleagues and would erode the high quality of the U.S. training system.

Gabriella Varallo Bedarida, MD, PhD
LMU University of Munich Innenstadt Hospital
80336 Munich, Germany

References

TO THE EDITOR: I disagree with Dr. Charap’s argument that the new work hour regulations for residents are “harmful to the future of our profession” (1). Dr. Charap believes that the new system suggests continuity is not important and rewards unprofessional behavior. What he fails to recognize is that the ACGME regulates work hours, not professionalism. Setting a standard for professional attitude and behavior is the responsibility of all of us in the profession. While the new work hour regulations undoubtedly present a significant challenge for program directors nationwide, they also bring new opportunities for medical educators to take an active role in teaching and promoting professionalism, rather than leaving it in the hidden curriculum where it has been for many years.

Sarang Kim, MD
University of Medicine and Dentistry of New Jersey–Robert Wood Johnson Medical School
New Brunswick, NJ 08903
TO THE EDITOR: In his recent commentary on reducing resident work hours (1), Dr. Charap argued that the ACGME should reconsider mandatory restrictions on resident work hours because they may result in reduced continuity of care, tarnished medical professionalism, and eroded investment in the medical community. I agree these are important dangers posed by the new hours restrictions; in fact, as a recent chief resident intimately involved in changing residency programs in response to the new regulations, I too have seen each of these risks realized. However, I believe that the proper response to these challenges is creative and long-overdue change in the way we educate medical residents, not a retreat to a blatantly broken status quo. Since more reasonable work hours and shared patient responsibilities are common facts of life after residency and themselves risk reduced continuity of care, we must do a better job of teaching our residents how to relay information about shared patients. Furthermore, we must model professional responsibility better and expect even more dedication of our well-versed pupils. Last, if residents are more satisfied with a fulfilling new career that is more reasonably balanced with life away from patients, they will be pulled toward the medical community. If not, we need to do a better job of addressing their needs. It will be challenging and time-consuming to reduce the risks of programmatic change in internal medicine education. These dangers will not be alleviated, however, by returning to the well-intentioned but erroneous belief that insufficient sleep and life imbalance result in personal happiness or improved patient care.

Timothy Lahey, MD
Beth Israel Deaconess Medical Center
Boston, MA 02215

Reference

TO THE EDITOR: We are concerned that the 4 essays on residents’ work hours (1–4) imply that all current trainees support shift work and that only the aged establishment is divided over the issue of resident work hours regulation. We are recent chief residents of New York City internal medicine residency programs who served during the first year of state-contracted work hour inspections. As attending physicians, we now oversee residents who from the start of internship have been literally commanded to leave the hospital at the strike of the clock. We see a nontrivial minority of trainees with marginal baseline commitment to patient care who believe that their work ethic is appropriate. We see dedicated trainees staying beyond their allotted hours to maintain continuity of care for acutely ill patients, potentially jeopardizing our institutions’ ongoing efforts to maintain compliance. We see increasing numbers of patient handoffs lead to troublingly frequent lapses in information transfer and subsequent quality of care.

The best patient care, and therefore the best medical training, must include continuity of care within reasonable limits. Although those limits have been continually reevaluated, only now have they become so strictly and externally mandated. Few lament the loss of the 110-hour work weeks and 48-hour shifts that even in our recent history were fact and not lore for surgery residents. Reevaluation is always ongoing and healthy, but current ACGME regulations are bluntly applied to the point of harm.

We eagerly await more data documenting the effects of long work hours and frequent patient handoffs on quality of care and anticipate that in moderation, the risks of the latter outweigh the risks of the former. We are all witnessing precedents that challenge the future of our profession, as the residents trained under these new regulations will one day inherit the leadership of medicine. We agree with Dr. Schroeder that the way we respond to these regulations will determine the future of medicine as a profession (4). These are not solely the concerns of “seasoned, male faculty members” (4).

Yungpo Bernard Su, MD
Memorial Sloan-Kettering Cancer Center
New York, NY 10021

Lydia Kang, MD
New York University Medical Center/Bellevue Hospital Center
New York, NY 10016

References

TO THE EDITOR: The papers on resident work hour reform by Charap (1), Skeff (2), and Glines (3) make valid yet conflicting observations. They illustrate the lack of historical data on the complex issues surrounding fatigue, sleep deprivation, and performance among residents. One reason for work hour reform was to mitigate the fatigue and perceived decrements in job performance that occur from excessive time on task. By reducing time at work and by mandating the education of housestaff and faculty about the effects of sleep deprivation, these reforms would reduce medical errors and other untoward effects of acute and chronic sleep deprivation. Unfortunately, a survey of more than 3000 residents from 21 specialties performed before work hour reforms were instituted showed that the correlation between work hours and sleep hours was less robust than previously thought (4). We suspect that resident physicians are not using their free time for sleep to repair their sleep debt. While education about specific fatigue management strategies is helpful, it is impossible to mandate sleep quantities for resident physicians outside the hospital. In addition, many residents report sacrificing sleep on call to accomplish their patient care responsibilities within the 24-hour-plus-6-hour limit. This is in direct contrast to the belief widely held in the sleep medicine community that the best countermeasure for sleepiness is sleep. Operational short naps of 20 minutes to 2 hours while on call can acutely improve alertness and functioning (5). We believe that a formal evaluation of this process is warranted and that countermeasures used in other 24-hour industries, such as mandatory nap periods, should be investigated for feasibility and outcomes in resident physicians. Such an approach would allow sys-

www.annals.org
Letters

Systematic improvement in resident alertness and performance that ultimately will increase patient safety.

Irene M. Rosen, MD
Judy A. Shea, PhD
Lisa M. Bellini, MD
University of Pennsylvania School of Medicine
Philadelphia, PA 19104

References

IN RESPONSE: Dr. Bedarida laments the effects of the work hour regulations. She has already noted a loss of care continuity and a real change in the attitude of residents, some of whom appear preoccupied with getting out of the hospital. She suggests that our new graduates will be ill-prepared after 3 years of training and contends that they, like their European counterparts, will need to work closely with senior physicians for several years to acquire the necessary skills for independent practice. I share her concern and have observed a lack of clinical maturity in a greater percentage of recent graduates.

Dr. Lahey recognizes that there will be difficulties in implementing these new regulations and suggests that we need to develop better signout systems to reduce errors. I agree with both points. However, I am not certain whether resident satisfaction or professional dedication will be enhanced by the regulations. I have observed the opposite to be the case.

In the 1990s, the ACGME Residency Review Committee for Internal Medicine had the following statement in its program requirements: “Physicians must have a keen sense of personal responsibility for maintaining patient care, and must recognize that their obligation to patients is not automatically discharged at any given hour of any particular day of the week. In no case should the resident go off duty until the proper care and welfare of the patient is ensured” (1).

Is this paragraph controversial? Are there physicians who disagree? It was eliminated when the new work hour regulations were mandated. Its omission serves as a startling confirmation of the shift in priorities. We must work to restore and maintain this basic principle.

Mitchell Charap, MD
New York University School of Medicine
New York, NY 10016

Corticosteroids for Septic Shock

TO THE EDITOR: The editorial by Dr. Luce (1) accompanying our meta-analysis examining clinical trials of low-dose steroid therapy in sepsis (2) raised concerns about our recommendation to administer low-dose glucocorticoids to all patients with vasopressor-dependent septic shock. Dr. Luce concluded that the results of the clinical sepsis trials of low-dose steroids support administering steroids only to patients with “proven adrenal insufficiency” (1). As cited by Dr. Luce, a recent report by Hamrahian and colleagues (3) demonstrated that in critically ill patients, variations in total serum cortisol measurements may be explained by differences in the concentration of serum binding proteins, and only free serum cortisol measurements accurately reflect adrenal function in these patients. In light of these findings, the division of patients into subgroups based on the results of corticotropin stimulation testing using total serum cortisol measurements may be inappropriate. Furthermore, these data support evaluating the overall effects of steroids in each of the clinical sepsis trials rather than focusing on subgroup analyses based on corticotropin stimulation tests using total serum cortisol measurements.

Each of the 5 low-dose steroid trials analyzed in our meta-analysis demonstrates a beneficial effect of steroids on mortality, shock reversal, or both (4–8). The marked consistency of the results of these 5 trials of low-dose steroid therapy (I² = 0%), while unusual in sepsis research, provides substantial evidence of the effectiveness of this therapy. This is even more remarkable given that the studies were relatively small and performed in different medical centers. Moreover, even though 1 of the 5 studies was much larger than the rest, it did not have excessive influence on the overall results (4). In fact, when this larger study is removed from the analysis, low-dose steroids still have a significant beneficial effect on survival (relative survival benefit, 1.36 [95% CI, 1.04 to 1.79]; P = 0.03). With regard to Dr. Luce’s concerns, our meta-analysis showed that steroids had consistent beneficial effects on both survival and shock reversal when patients were divided into responders or nonresponders. In fact, the overall effects of steroids on these subgroups were indistinguishable in the 3 trials that reported this subdivision (Table) (4, 5, 8).

We believe that our meta-analysis revealed a consistent and overall statistically significant beneficial effect of steroids on survival and shock reversal, regardless of corticotropin stimulation testing results. Therefore, we recommended that “unless further clinical sepsis trials demonstrate that responders do not benefit from therapy, steroids should be considered for all patients with vasopressor-dependent septic shock” (2). As Dr. Luce discussed, an ongoing randomized, controlled trial, CORTICUS, has randomly assigned 800 patients to receive low-dose steroid therapy or placebo. Given the results of our meta-analysis and the insight provided by Hamrahian and colleagues, we feel that the CORTICUS data safety and monitoring board should perform an interim analysis to evaluate whether the trial should continue in its current form, be altered to evaluate only the subgroup of responders who have no conclusive data on

Reference

Downloaded From: http://annals.org/ on 10/25/2018
outcome, accept a higher $P$ value for benefit if the results are consistent with those of previous studies, or be discontinued. Such an interim analysis may prevent the inadvertent withholding of a beneficial therapy to critically ill patients in septic shock.

Peter C. Minneci, MD
Katherine J. Deans, MD
Steven M. Banks, PhD
Peter Q. Eichacker, MD
Charles Natanson, MD
National Institutes of Health
Bethesda, MD 20892

References

CLINICAL OBSERVATION

Tadalafil in Primary Pulmonary Arterial Hypertension

TO THE EDITOR: Background: Sildenafil, a short-acting phosphodiesterase-5 inhibitor (1), is safe and may benefit patients with primary pulmonary arterial hypertension (2–8). However, it requires many daily administrations. We describe a patient with end-stage primary pulmonary arterial hypertension who improved while taking tadalafil, a long-acting phosphodiesterase-5 inhibitor (9).

Case Report: A 72-year-old woman was hospitalized for progressive cardiopulmonary failure. Five years earlier, primary pulmonary arterial hypertension was diagnosed and the patient was hospitalized for hydropic decompensation and hypoxemia. Since then, she had been receiving permanent oxygen therapy and had also taken digoxin, amlodipine, furosemide, potassium canrenoate, and acenocoumarol.

At the most recent hospitalization, the patient had dyspnea (New York Heart Association class IV) and $+$ pitting edema of the legs up to the thighs, which had progressed over the previous 3 months. The patient’s blood pressure was 110/70 mm Hg, her pulse was 102 beats/min, her respiratory frequency was 32 breaths/min, and her temperature was 36.8 °C. During oxygen therapy (fraction of inspired oxygen, 35%), arterial $P_{O_2}$ was 55 mm Hg. Electrocardiography showed sinus rhythm and right ventricular hypertrophy. Chest radiography showed cardiomegaly without signs of pulmonary edema. Doppler echocardiography showed dilation of right chambers with severe tricuspid regurgitation and estimated peak systolic pulmonary pressure of 105 mm Hg. Chest spiral computed tomography excluded pulmonary arterial embolism.

Despite administration of intravenous diuretics and optimization of oxygen therapy, the patient’s condition did not substantially improve. Epoprostenol therapy was attempted but was stopped because the patient had symptomatic arterial hypotension despite a low infusion rate. Therefore, with the patient’s informed consent, we administered tadalafil (20 mg orally every other day) in addition to background therapy.

After 2 weeks of tadalafil therapy, the patient improved remarkably (New York Heart Association class II); the only untoward effect was slight arterial hypotension that promptly regressed with amlodipine withdrawal. Blood pressure was 116/66 mm Hg, pulse rate was 84 beats/min, and respiratory frequency was 20 breaths/min. Leg edema was remarkably reduced. The patient’s arterial $P_{O_2}$ was 70 mm Hg during oxygen therapy (fraction of inspired oxygen, 0.28%). Doppler echocardiography showed a notable reduction of the estimated peak systolic pulmonary pressure (80 mm Hg). Accordingly, doses of intravenous diuretics were progressively decreased and were administered orally. The patient was discharged and referred to outpatient care.

After 6 months of tadalafil treatment, the patient’s functional status improved (New York Heart Association class II). Physical examination showed normal heart rate and respiratory frequency, and disappearance of leg edema. Arterial $P_{O_2}$ during oxygen therapy (fraction of inspired oxygen, 0.24%) remained stably above 70 mm Hg. Doppler echocardiography showed progressive reduction of estimated peak pulmonary systolic pressure (up to 65 mm Hg). Accordingly, we reduced oral doses of diuretics and prescribed oxygen therapy only during physical activity.

Table. Overall Effects of Low-Dose Steroids Based on Corticotropin Stimulation Testing Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Nonresponders (Events/Total Patients)</th>
<th>Steroid Group, % (n/n)</th>
<th>$P$ Value</th>
<th>Responders (Events/Total Patients)</th>
<th>Steroid Group, % (n/n)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>63 (83/132)</td>
<td>51 (63/123)</td>
<td>0.05</td>
<td></td>
<td>57 (32/56)</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>Shock reversal</td>
<td>39 (48/123)</td>
<td>53 (63/118)</td>
<td>0.03</td>
<td></td>
<td>44 (20/45)</td>
<td>&gt;0.2</td>
</tr>
</tbody>
</table>

TO THE EDITOR: Background: Sildenafil, a short-acting phosphodiesterase-5 inhibitor (1), is safe and may benefit patients with primary pulmonary arterial hypertension (2–8). However, it requires many daily administrations. We describe a patient with end-stage primary pulmonary arterial hypertension who improved while taking tadalafil, a long-acting phosphodiesterase-5 inhibitor (9).

Case Report: A 72-year-old woman was hospitalized for progressive cardiopulmonary failure. Five years earlier, primary pulmonary arterial hypertension was diagnosed and the patient was hospitalized for hydropic decompensation and hypoxemia. Since then, she had been receiving permanent oxygen therapy and had also taken digoxin, amlodipine, furosemide, potassium canrenoate, and acenocoumarol.

At the most recent hospitalization, the patient had dyspnea (New York Heart Association class IV) and $+$ pitting edema of the legs up to the thighs, which had progressed over the previous 3 months. The patient’s blood pressure was 110/70 mm Hg, her pulse was 102 beats/min, her respiratory frequency was 32 breaths/min, and her temperature was 36.8 °C. During oxygen therapy (fraction of inspired oxygen, 35%), arterial $P_{O_2}$ was 55 mm Hg. Electrocardiography showed sinus rhythm and right ventricular hypertrophy. Chest radiography showed cardiomegaly without signs of pulmonary edema. Doppler echocardiography showed dilation of right chambers with severe tricuspid regurgitation and estimated peak systolic pulmonary pressure of 105 mm Hg. Chest spiral computed tomography excluded pulmonary arterial embolism.

Despite administration of intravenous diuretics and optimization of oxygen therapy, the patient’s condition did not substantially improve. Epoprostenol therapy was attempted but was stopped because the patient had symptomatic arterial hypotension despite a low infusion rate. Therefore, with the patient’s informed consent, we administered tadalafil (20 mg orally every other day) in addition to background therapy.

After 2 weeks of tadalafil therapy, the patient improved remarkably (New York Heart Association class II); the only untoward effect was slight arterial hypotension that promptly regressed with amlodipine withdrawal. Blood pressure was 116/66 mm Hg, pulse rate was 84 beats/min, and respiratory frequency was 20 breaths/min. Leg edema was remarkably reduced. The patient’s arterial $P_{O_2}$ was 70 mm Hg during oxygen therapy (fraction of inspired oxygen, 0.28%). Doppler echocardiography showed a notable reduction of the estimated peak systolic pulmonary pressure (80 mm Hg). Accordingly, doses of intravenous diuretics were progressively decreased and were administered orally. The patient was discharged and referred to outpatient care.

After 6 months of tadalafil treatment, the patient’s functional status improved (New York Heart Association class II). Physical examination showed stable normotension, further reduction of heart rate and respiratory frequency, and disappearance of leg edema. Arterial $P_{O_2}$ during oxygen therapy (fraction of inspired oxygen, 0.24%) remained stably above 70 mm Hg. Doppler echocardiography showed progressive reduction of estimated peak pulmonary systolic pressure (up to 65 mm Hg). Accordingly, we reduced oral doses of diuretics and prescribed oxygen therapy only during physical activity.

Table. Overall Effects of Low-Dose Steroids Based on Corticotropin Stimulation Testing Results

| Outcome         | Nonresponders (Events/Total Patients) | Steroid Group, % (n/n) | $P$ Value | Responders (Events/Total Patients) | Steroid Group, % (n/n) | $P$ Value |
|-----------------|--------------------------------------|------------------------|----------|                                    |                        |          |
| Control Group   |                                       |                        |          |                                    |                        |          |
| Death           | 63 (83/132)                           | 51 (63/123)            | 0.05     |                                    | 57 (32/56)             | >0.2     |
| Shock reversal  | 39 (48/123)                           | 53 (63/118)            | 0.03     |                                    | 44 (20/45)             | >0.2     |
Discussion: By stabilizing guanosine 3',5'-cyclic monophosphate in vascular smooth-muscle cells of the pulmonary artery, sildenafil prolongs the effect of endogenous vasodilators. Through this mechanism, it reduces mean pulmonary artery pressure and the pulmonary-to-systemic vascular resistance ratio and improves the overall ventilation–perfusion mismatch, arterial oxygenation, and functional capacity (3–8). However, because it has a half-life of about 4 hours (1), sildenafil requires many daily administrations, which in the long term may compromise treatment adherence and may be costly.

In our patient with end-stage primary pulmonary arterial hypertension, we observed that long-term treatment with tadalafil, which has a half-life of about 18 hours, was safe and greatly improved pulmonary hemodynamics and arterial oxygenation (Figure). These improvements were paralleled by a striking improvement in clinical and functional status. Besides confirming the efficacy of phosphodiesterase-5 inhibitors in treatment of primary pulmonary arterial hypertension, this finding may alert physicians to the possibility that tadalafil may be more affordable than sildenafil. In fact, because its half-life is nearly 5-fold greater than sildenafil’s (9), tadalafil may be administered once daily or even every second day, a feature that may improve adherence and reduce treatment costs.

Emiliano Antonio Palmieri, MD
Flora Affuso, MD
Serafino Fazio, MD
University Federico II Medical School
80131 Naples, Italy

Danilo Lembo, MD
Eli Lilly
50019 Florence, Italy

References

CORRECTIONS

Correction: Update in Gastroenterology and Hepatology

In a recent Update (1), the title of Table 1 should have read “Current Status of Drug Therapy for Inflammatory Bowel Disease.”

Reference

Correction: Screening for Chlamydia trachomatis in Women 15 to 29 Years of Age

In an article on screening for Chlamydia trachomatis in women 15 to 29 years of age (1), Table 1 contained an error. Under the heading “Quality of life,” “Asymptomatic acute urogenital chlamydial infection” should have read “Symptomatic acute urogenital chlamydial infection.”

Reference
To Butterfly or To Needle: The Specimen Testing Question

TO THE EDITOR: The letter by Heffler and colleagues (1) on the butterfly collection device for venipuncture was quite interesting, and the results were not surprising. I would like to know, however, the outcome of the testing of each specimen. Were there more problem specimens (hemolysis, insufficient quantity) in the butterfly cohort than in the conventional needle group? The goal of good venipuncture technique is not only patient comfort but also the collection of optimal blood specimens. If use of the butterfly device results in more problem specimens, then the reduction in discomfort is a false gain.

William M. Miller, MD
Quest Diagnostics
Tucker, GA 30084

Reference

IN RESPONSE: We thank Dr. Miller for his comment on our letter. As he pointed out, specimen quantity and quality are probably as important as venipuncture success rates and patient discomfort. On the basis of our study, we can address only specimen quantity. We noted failure of blood collection when a second venipuncture had to be performed, for whatever reason, to fill all blood tubes. If problems with specimen quantity had arisen because the butterfly device led to additional venipuncture attempts, we would have noticed an increased failure rate with the butterfly device. Because we observed a decreased failure rate, we can almost completely exclude the possibility that specimen quantity problems might be linked to the butterfly device.

Anecdotally, blood collection with the butterfly device has been linked to an increased rate of hemolysis compared with the conventional needle (1). No scientifically founded data on this topic have been provided to date. Our study was not designed to answer this particular question. Of note, only a fraction of laboratory values are measured inexacty in the presence of hemolysis. For most clinical questions, hemolysis at blood collection, although undesirable, does not significantly alter laboratory values or clinical decision making. Therefore, we believe that answering the hemolysis question is of clinical value but does not significantly impact the results of our study.

Lukas Heffler, MD
Medical University Vienna
A-1090 Vienna, Austria

Reference