process, and in what manner they would like the treatment to continue, if at all. Obviously, it is more appropriate if the surrogate can be found before the decision to treat is made.

The central issue in these very cases, in which they are resolved well, seems to be the involvement of the health-care surrogate as early and as rapidly as possible. This is not simply passing the responsibility off to another person. Rather, it is taking into account the considerations of an individual that the patient has considered “of confidence.” Additionally, and as has been argued in the past, in the context of a different iteration of the problem of autonomy, to not do our utmost to follow our patient’s central moral beliefs results in paternalism:

The harmful consequences of [which] would affect not only the patient. The physician also would bear a heavy and unnecessary responsibility to adjudicate a patient’s preferences and moral beliefs, and to determine for each one not only the appropriate treatment... but also the patient’s ultimate interests. Besides mistakes medical judgments that can result from not knowing a patient’s preferences, the physician would be unlikely to know what would constitute a patient’s best interest, and yet the physician would bear the burden of responsibility for any error that occurs. Communication between patient and caregiver, already difficult, becomes even more complicated when decisions about deeply held precepts are adjudicated privately by the physician.

Finally, one cannot help but wonder where the social workers are in the cases described? These members of our health-care team, the so-called “ancillary help,” have been ravaged by cost cutting in medicine. Without their aggressive assistance and input, the help that the health-care team can provide is lessened. Could this be another of the issues that must be addressed in the problem of enigmatic refusal?

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Obstructive Sleep Apnea and Platelet Activation
Another Potential Link Between Sleep-Disordered Breathing and Cardiovascular Disease

Cardiovascular disease is the most frequent cause of morbidity and mortality in the industrialized world.1,2 Obstructive sleep apnea (OSA) is also highly prevalent, estimated to affect >15 million individuals in the United States.3 Accordingly, cardiovascular disease and OSA frequently coexist. This association may not be coincidental or due to confounding comorbidities. Longitudinal1 and cross-sectional1,3,5 epidemiologic data support the concept that OSA is an independent risk factor for hypertension, stroke, coronary artery disease, and congestive heart failure. These observations have prompted investigations of the role of sleep in cardiovascular disease pathogenesis.

Non-rapid eye movement sleep typically accounts for 85% of total sleep time in healthy adults, and is a state of hemodynamic and autonomic quiescence. In contrast, the cardiovascular system is abruptly disturbed by the recurrent hypoxemia, hypercapnia, exaggerated intrathoracic pressure swings, and arousals that characterize obstructive apneas/hypopneas.6 Sharp increases in heart rate and BP result from phasic increases in sympathetic neural activity.7 Multiple, potentially intertwined mechanisms are proposed to etiologically link OSA with chronic cardiovascular disease, including tonic elevation of sympathetic neural activity, vascular endothelial dysfunction, oxidative stress, inflammation, and metabolic dysregulation.6 Repetitive surges of sympathetic neural activity, as well as cascades of increased concentrations of vasoactive peptides and proinflammatory factors may directly promote endothelial injury and vascular events.

Another purported connection between OSA and
cardiovascular disease is enhanced coagulability, possibly mediated by enhanced sympathetic neural activation.\textsuperscript{8–12} The circadian distribution of cardiovascular and vascular events strongly suggests an interaction between sleep, arousal, and acute thrombosis. Myocardial infarction and sudden death exhibit a peak occurrence between 6 AM and 11 AM.\textsuperscript{13} Platelets play a key role in ischemic cardiovascular disease and increases in platelet aggregability and activation\textsuperscript{8–12} have been demonstrated in patients with OSA. In addition, increases in hematocrit,\textsuperscript{14} blood viscosity,\textsuperscript{15} and fibrinogen\textsuperscript{16} have also been documented in OSA and may predispose to hypercoagulability. Hence, OSA may act through multiple mechanisms to predispose to cardiovascular disease and acute thrombosis. There have been limited reports\textsuperscript{17,18} addressing the degree to which potentially atherogenic and prothrombotic neural, vasoactive, and inflammatory mechanisms may be altered by continuous positive airway pressure (CPAP).

Within this context of an ever-increasing appreciation of the mechanistic relationship between OSA and cardiovascular disease comes the report of Hui and colleagues.\textsuperscript{19} They confirm increased platelet activation in a cohort of 42 patients with OSA (apnea-hypopnea index > 10) compared to a non-OSA, age- and body mass index-matched control group, with the arousal index being the independent factor best associated with baseline platelet activation. They also demonstrate that CPAP treatment incrementally reduced platelet activation at 1 night and 3 months. These observations lend further credence to the notion that OSA is associated with increased cardiovascular risk, as well as support a pathophysiologic paradigm of sleep arousal precipitating increased sympathetic neural activation leading to increased platelet activation. The observation that CPAP reduces platelet activation supports this same paradigm and suggests that treatment intervention for OSA may be cardioprotective.

The case-controlled design limits interpretation of the data. However, a case-controlled design may be most appropriate for a mechanistic study otherwise requiring randomization to no CPAP in patients with symptomatic OSA. Single morning measurements of platelet activation also leaves open the question as to whether increases are due to chronic untreated OSA, or reflect only the acute and transient effects of overnight hypoxia. There are a paucity of subjects with very increased platelet activation and severe OSA (Fig 1 of Hui et al\textsuperscript{19}), so that the regression analyses describe only a small number of such affected individuals. The study also does not account for those patients in whom severe OSA is not associated with increased platelet activation (Fig 1). The strength of association described between OSA and increased platelet activation is modest, and no causality is demonstrated. One wonders if the reduction in platelet activation would have been more dramatic had CPAP compliance been greater (mean objectively documented use was 3.9 ± 1.9 h/night [± SD]). Thus, the evidence is circumstantial, albeit provocative, and more robust data will be needed to convincingly demonstrate the potential clinical relevance of these observations. Lastly, not known is whether other indices of platelet function are similarly affected, and how the abnormalities noted would relate to actual incident cardiovascular events.

Nevertheless, the study raises important issues, both mechanistic and therapeutic. If platelet activation can be reduced by CPAP in the management of OSA, will this lower the frequency of cardiovascular events? Would such a benefit of CPAP be incremental to the effects of antiplatelet therapy, including aspirin and clopidogrel (especially in patients with known coronary artery disease)? The epidemic of obesity in the United States is no doubt associated with consequent increased prevalence of OSA, which may often be present even in nonsleepy individuals. If CPAP lowers risk for cardiovascular events, the criteria for implementation of CPAP therapy may need to be expanded to include intervention for nonsleepy individuals with OSA. Clearly, to justify such therapeutic approaches will require prospective, patient-oriented investigation to further elucidate mechanisms of disease pathogenesis as well as larger controlled and randomized trials to test treatment strategies. Such approaches will require close collaboration between specialists in both sleep disorders and cardiovascular disease.

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