

protect against lung injury in this clinical setting, but it seems unlikely.

After almost 40 years of searching unsuccessfully for effective strategies to prevent bronchopulmonary dysplasia, it would be a welcome surprise if a simple pharmacologic intervention proved to reduce its incidence. The findings of Schmidt et al. suggest the possibility that caffeine may have this effect, at least in infants who do not require prolonged intubation. However, neonatologists must not repeat the same mishap that occurred with the use of corticosteroids in preterm infants to prevent bronchopulmonary dysplasia, which resulted in worse long-term neurologic outcomes. The primary outcomes of the caffeine trial (i.e., long-term outcomes) are still pending. Assessment of the long-term effects of caffeine is needed before this therapy can be routinely recommended to prevent bronchopulmonary dysplasia.

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## Imaging Progression in Polycystic Kidney Disease

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Autosomal dominant polycystic kidney disease (ADPKD), a condition characterized by massively enlarged kidneys containing fluid-filled cysts, profoundly affects those who inherit one of the known genes that cause the disease. Mutations in the polycystic kidney disease 1 gene (*PKD1*), located on chromosome 16, account for approximately 85 percent of cases; the remaining 15 percent are due to mutations in the polycystic kidney disease 2 gene (*PKD2*), located on chromosome 4.<sup>1</sup> Progressive kidney dysfunction, hypertension, abdominal and flank pain, gross hematuria, and nephrolithiasis are frequently observed in this condition. Extrarenal manifestations that include intracranial aneurysms, hepatic cysts, cardiac valvular disease, and an increased risk of cardiovascular disease associated with chronic kidney disease may result in further illness and death.<sup>2</sup> Adding to the pain and suffering associated with

the extensive renal and extrarenal manifestations of ADPKD, the protean manifestations of ADPKD go beyond the index patient, owing to the autosomal dominant inheritance of the condition. Thus, a parent, child, sibling, and other members of the extended family have a 50 percent chance of being affected.

Previous efforts to find therapies to delay the progression of kidney disease at an early stage in ADPKD have been unsuccessful.<sup>3,4</sup> Although it is possible that the therapeutic agents studied in previous interventions truly had no effect on disease progression, such negative studies were probably underpowered as a result of small sample sizes; they also may have failed to detect a real benefit, because the glomerular filtration rate (GFR) deteriorates very slowly in the early stages of the disease, making the effects of tested therapies difficult to evaluate. Interventions in rela-

tively advanced disease, when rapid decline in the GFR occurs, have not slowed the rate of decline.<sup>5,6</sup>

Measuring the GFR alone has not been sufficient for the assessment of changes in early ADPKD. For example, a previous study demonstrated a rate of decline in the GFR of 2 to 3 ml per minute per year in normotensive persons with ADPKD whose mean baseline GFR was 112 ml per minute<sup>7</sup>; this is a small change that might render the detection of benefit difficult. Thus, a tool that detects small changes in ADPKD early enough has been needed.

Assessments of both the prognosis of affected patients and the effectiveness of therapies have been problematic in ADPKD. In this issue of the *Journal*, Grantham et al.<sup>8</sup> report on the results of serial assessment of the total volume of kidneys and cysts in 232 patients with ADPKD who had preserved renal function at baseline. For this assessment, the investigators used magnetic resonance imaging (MRI) and quantitative image analysis in parallel with GFR measurements.<sup>8</sup> The study demonstrates that kidney growth occurs in an exponential fashion and that the growth of kidneys in patients with ADPKD is primarily the result of the growth of cysts. Thus, it appears that the growth of cysts is the outcome of the disease, not a surrogate outcome. An unexpected finding of the study was that both kidneys in most patients with the disease were observed to grow at similar rates. A detailed analysis of the results of the study indicates that more rapid rates of growth of cysts and a decrease in the GFR are evident in kidneys that have a baseline volume of more than 1500 ml, regardless of the age of the patient. As might be anticipated from the earlier age at the development of end-stage renal disease among patients with *PKD1* mutations,<sup>1</sup> the kidneys of patients with *PKD1* mutations are larger and grow more quickly than do the kidneys of patients with *PKD2* mutations. Thus, MRI assessment of kidney volume appears to be promising for the identification of patients at risk for loss of GFR and perhaps will prove to be a useful tool for the assessment of interventions.

The study by Grantham et al. — which was part of the Consortium for Radiologic Imaging Studies in Polycystic Kidney Disease (CRISP), sponsored by the National Institutes of Health (NIH) — documents that the growth of kidneys and cysts in patients with ADPKD who have well-

preserved kidney function is predictable and can be measured in a reliable and reproducible fashion. The availability of this volumetric method may provide a timely way to evaluate a number of potential therapies that may slow the rate of deterioration of renal function in ADPKD — for example, agents that block the renin–angiotensin–aldosterone system,<sup>9</sup> an antagonist of the vasopressin V2 receptor that interrupts the synthesis of cyclic AMP,<sup>10</sup> long-acting somatostatins,<sup>11</sup> and sirolimus.<sup>12</sup> Future clinical trials will probably incorporate assessment of the total volume of kidneys and cysts as seen on MRI as a primary outcome. In fact, the ongoing NIH-sponsored Halt Progression of Polycystic Kidney Disease (HALT-PKD) study is using MRI assessment of the total kidney volume as a primary outcome ([www.pkdwustl.edu/pkd-tn/](http://www.pkdwustl.edu/pkd-tn/)). A demonstration of significant slowing of the rate of growth of kidneys and cysts by a therapeutic agent in a randomized, prospective clinical trial might arguably be considered definitive by many clinicians. However, the use of the growth of kidneys and cysts as a primary end point of a therapeutic trial still requires long-term validation with concomitant assessment of additional outcomes, including the GFR, progression to end-stage renal disease, and other identifiable complications.

Is there a role for MRI assessment of total kidney volume as part of routine clinical care for patients with ADPKD? According to the findings of Grantham et al., patients whose kidneys have a volume larger than 1500 ml have a worse prognosis, with a more rapid decline in the GFR and probably earlier development of end-stage renal disease. That said, with our present limited therapeutic armamentarium, changes in therapy would not be driven by the knowledge of the total volume of kidneys and cysts. It is possible, perhaps even likely, that the effectiveness of new therapeutic agents will differ among patients with ADPKD who have smaller kidneys and those who have larger kidneys. Only rigorous and controlled studies that test specific therapies and use techniques that accurately measure the growth of kidneys and cysts, as described by Grantham et al., will be able to provide this information.

It is important to recognize that such detailed techniques for the analysis of three-dimensional images are not routinely available in clinical radiology departments, nor is reimbursement available for the extra effort involved in the measure-

ment of the volume of kidneys and cysts. Thus, at present, quantitative assessment of kidney volume with the use of MRI remains a research procedure, albeit a substantial potential addition to our ability to determine the effect of therapeutic interventions on renal progression in this challenging disease.

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