Contrast-enhanced Magnetic Resonance Imaging Does Not Detect a Progression in Lung Morphological Score in Preschool Children with Cystic Fibrosis

To the Editor:

We have read with interest the study by Stahl and colleagues about the use of lung magnetic resonance imaging (MRI) in preschool children with cystic fibrosis from 0 to 4 years of age (1). Using multiple comparison statistical tests across patients from 0 to 4 years of age, the authors concluded that MRI could allow early detection of modifications over time, which were ascribed to the progression of the lung disease. However, two major limitations are not discussed in the text.

First, the authors provide an overall *P* value of multiple comparison analyses in the main manuscript. However, a more extensive description of how these statistical tests were obtained was made available in Tables E7 and E8 in their online supplement. Interestingly, there was no difference in any of their biomarker analyses from 1 to 4 years of age (Table E7). All statistical tests in those preschool children between 1 and 4 years of age found no significant longitudinal variation over that time.

The only differences were found when comparing the patients at 1–4 years of age with the patients at 0 years of age. This finding deserves some comment, as it is not discussed as a major limitation of the study. Indeed, at 0 years of age, only 20 out of 48 (41%) patients could undergo a contrast material injection because of ethical issues. Conversely, 91–100% had a contrast-enhanced MRI scan between 1 and 4 years, using an additional gadolinium chelate injection ($P < 0.001$). It is common knowledge that non–contrast-enhanced and contrast-enhanced MRI are noncomparable imaging modalities (2–4). As expected, an injection of contrast MRI does increase the visibility of morphological abnormalities using lung MRI, most notably wall thickening and bronchiectasis (2–4).

Second, there is another major limitation of this study. The comparisons were made using a repeated measure ANOVA. The statistical requirement of this test is to be performed in the same subjects over time. In Table E7, it looks like the comparisons were made in heterogeneously distributed patient groups, with various and different patients per group. This is confirmed and well documented in Table E8 of the article, demonstrating that the study groups at 0 to 4 years were composed of different children. Notably, there are 6 out of 48 (12%) children with late cystic fibrosis diagnosis at 0 years, versus 13 out of 35 (37%) children with late cystic fibrosis diagnosis at 4 years ($P < 0.001$). Conversely, there were 22 out of 48 children with ne8wborn screening (NBS) at 0 years (45%) versus 8 out of 35 children with NBS at 4 years (22%) ($P = 0.03$). Of note, two-thirds of the NBS population was not clinically stable enough to perform the lung MRI procedure, which contradicts the statement of a good clinical condition. Therefore, Figures 1 and 3 of the main article are reporting means and SDs from noncomparable and different patients (Table E8). Thus, Figures 1 and 3 do not correspond to longitudinal data from the same patients over time (Table E8).

To conclude, the lack of any variation in contrast-enhanced MRI from 1 to 4 years of age does not seem convincing data to promote the use of general anesthesia with contrast material injection once a year, in this age range. Regarding its use in newborns at 0 years to support NBS, a study that would not compare non–contrast-enhanced versus contrast-enhanced MRI would be appropriate. Indeed, better MRI visibility of wall thickening/bronchiectasis and morphology, thanks to a contrast material injection, is an expected finding. Also, a longitudinal study with comparison tests performed within the same patients over time is still lacking. ■

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Reply to Dournes *et al.*

From the Authors:

We thank Dournes and colleagues for their interest in our study on the longitudinal course of early cystic fibrosis (CF) lung disease

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detected by proton magnetic resonance imaging (MRI) (1) and for their comment regarding the analysis of the data from multiple time points. We investigated a cohort of 96 infants and preschool children with CF over the first 4 years of life by annual chest MRI scans, demonstrating that CF lung disease is present from the first year of life and progresses over time in these infants and preschool children under symptomatic standard of care (1). Furthermore, we were able to demonstrate that CF lung disease is less pronounced in infants and preschool children after a presymptomatic diagnosis by newborn screening than in infants and preschool children diagnosed due to clinical signs of CF (1). In addition to reporting the main analyses on the longitudinal course of our total cohort and the different diagnostic groups in the main manuscript (Figures 1 and 3 in Reference 1), we provided detailed information on the prevalence and extent of changes in lung structure and perfusion captured by the subscores of the morphofunctional MRI score according to age in years and diagnostic subgroups (Tables E7 and E8 in the online supplement in Reference 1). The analyses in Tables E7 and E8 are based on the Bonferroni *post hoc* test and compare distinct age groups. The preceding repeated measures ANOVA takes the entire observation period into account, and its main results are presented in the main manuscript (Figures 1 and 3 in Reference 1). Minor but persistent or only slowly increasing changes may not be statistically significant when comparing two distinct time points only but can lead to a significant difference with time (2). The strength of a repeated measures ANOVA with a within-subject analysis is the reduced variability of measurements and a decreased error with improved statistical power (3, 4).

Regarding the comment on the potential influence of the number of investigations performed without versus with application of contrast material in infants and preschool children, it is noteworthy that the rating of most morphological abnormalities by the MRI score (i.e., mucus plugging, sacculation, consolidation, and pleural reaction) used in our present and previously published studies is performed in non–contrast-enhanced T1-weighted sequences in conjunction with T2-weighted sequences and can therefore be compared in all patients independent of contrast material application (1, 5–9). Of note, T2 weighting is always acquired before contrast injection and thus a completely contrast-independent measure. Despite a reduced number of contrast-enhanced MRI scans in infants due to the late approval of its use in this age group in Germany, the differences and the increase in morphological MRI scores remain constant in the following years when application of contrast material is consistently used. These results are in line with a previous cross-sectional study and underscore the longitudinal progression of lung disease in young children with CF (9).

Regarding the children investigated in our study and the definition of the late clinical diagnosis group (LCD), we used an age $>$4 months as a cutoff against the early clinical diagnosis group, as it is well known from previous studies that a majority of infants already show morphological features of CF lung disease at that time (9–11). Some children of the LCD group were recruited in the study after their first birthday (and after making the late diagnosis), explaining the discrepancy between the participant numbers in the LCD group at different time points. Similarly, some infants participating after diagnosis by newborn screening or early clinical diagnosis did not reach the age of 4 years during the study period. However, this study does not rely on two-sample tests (e.g., comparing MRI scores at the age of 0 and 4 yr) but is based on five time points and a longitudinal repeated measure ANOVA, providing a robust test for longitudinal observations with a varying number of data points at the different time points, including the same subjects over multiple consecutive years (1, 3, 4). As mentioned in the supplemental methods in the online supplement, the results of this analysis were cross-validated using a generalized linear mixed model. This study therefore offers useful information on trajectories of CF lung disease in infants and preschool children, demonstrating a significant progression of CF lung disease by longitudinal MRI studies in our cohort from birth to the age of 4 years (1).

In contrast to other diagnostic procedures, such as controlled ventilation computed tomography and BAL, chest MRI in infants and preschool children with CF can be performed with high success rates in sedation without the need of general anesthesia, even in a multicenter setting (1, 8, 9, 12, 13). The use of chloral hydrate for sedation without the necessity of invasive ventilation has been established, widely used, and safety approved in this age range (14, 15). We therefore appreciate MRI as a helpful tool for research on early lung disease and clinical care for improved diagnostic monitoring of infants and preschool children with CF. ■

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