

4. Chao MC, Rubin EJ. Letting sleeping *dos* lie: does dormancy play a role in tuberculosis? *Annu Rev Microbiol* 2010;64:293–311.
5. Garton NJ, Waddell SJ, Sherratt AL, Lee SM, Smith RJ, Senner C, Hinds J, Rajakumar K, Adegbola RA, Besra GS, et al. Cytological and transcript analyses reveal fat and lazy persister-like bacilli in tuberculous sputum. *PLoS Med* 2008;5:e75.
6. Mukamolova GV, Turapov O, Malkin J, Woltmann G, Barer MR. Resuscitation-promoting factors reveal an occult population of tubercle bacilli in sputum. *Am J Respir Crit Care Med* 2010;181:174–180.
7. Dhillon J, Fourie PB, Mitchison DA. Persister populations of *Mycobacterium tuberculosis* in sputum that grow in liquid but not on solid culture media. *J Antimicrob Chemother* 2014;69:437–440.
8. Tree JA, Williams A, Clark S, Hall G, Marsh PD, Ivanyi J. Intranasal bacille Calmette-Guérin (BCG) vaccine dosage needs balancing between protection and lung pathology. *Clin Exp Immunol* 2004;138:405–409.
9. Spratt JM, Britton WJ, Triccas JA. *In vivo* persistence and protective efficacy of the bacille Calmette Guérin vaccine overexpressing the HspX latency antigen. *Bioeng Bugs* 2010;1:61–65.
10. Kaprelyants AS, Mukamolova GV, Ruggiero A, Makarov VA, Demina GR, Shleeva MO, Potapov VD, Shramko PA. Resuscitation-promoting factors (Rpf): in search of inhibitors. *Protein Pept Lett* 2012;19:1026–1034.
11. Kana BD, Gordhan BG, Downing KJ, Sung N, Vostroknutova G, Machowski EE, Tsenova L, Young M, Kaprelyants A, Kaplan G, et al. The resuscitation-promoting factors of *Mycobacterium tuberculosis* are required for virulence and resuscitation from dormancy but are collectively dispensable for growth *in vitro*. *Mol Microbiol* 2008;67:672–684.
12. Shleeva MO, Kudykina YK, Vostroknutova GN, Suzina NE, Mulyukin AL, Kaprelyants AS. Dormant ovoid cells of *Mycobacterium tuberculosis* are formed in response to gradual external acidification. *Tuberculosis (Edinb)* 2011;91:146–154.
13. Biketov S, Mukamolova GV, Potapov V, Gilenkov E, Vostroknutova G, Kell DB, Young M, Kaprelyants AS. Culturability of *Mycobacterium tuberculosis* cells isolated from murine macrophages: a bacterial growth factor promotes recovery. *FEMS Immunol Med Microbiol* 2000;29:233–240.
14. Kolwijck E, Friedrich SO, Karinja MN, van Ingen J, Warren RM, Diacon AH. Early stationary phase culture supernatant accelerates growth of sputum cultures collected after initiation of anti-tuberculosis treatment. *Clin Microbiol Infect* 2014;20:O418–O420.
15. Huang W, Qi Y, Diao Y, Yang F, Zha X, Ren C, Huang D, Franken KL, Ottenhoff TH, Wu Q, et al. Use of resuscitation-promoting factor proteins improves the sensitivity of culture-based tuberculosis testing in special samples. *Am J Respir Crit Care Med* 2014;189:612–614.

Copyright © 2014 by the American Thoracic Society

Caffeine Therapy for Apnea of Prematurity: Long-Term Effect on Sleep by Actigraphy and Polysomnography



To the Editor:

Marcus and colleagues checked the long-term effects of caffeine therapy for apnea of prematurity by using actigraphy, polysomnography, and parental sleep questionnaire (1). Although the authors concluded that therapeutic neonatal caffeine administration had no long-term effects on sleep duration or sleep apnea during childhood, there was a discrepancy in sleep duration between results from actigraphy and polysomnography. Melzer and colleagues mentioned that actigraphy showed poorer specificity (to detect wake), and each researcher should adjust the scoring algorithm/sensitivity depending on age and the level of sleep disturbance (2). I suppose that the authors understand the limitation of actigraphy for sleep evaluation, but there was no precise description on the adjustment of actigraphy in the text or the online supplement. Meltzer and colleagues reported that actigraphy should be used with caution to keep specificity and sensitivity by adjusting the scoring

threshold of sensitivity of Actiwatch 2 (Philips Respironics, Bend, OR) (2, 3), which could be done by the setting through software. As Marcus and colleagues conducted the validation study with an epoch-by-epoch comparison of actigraphy and simultaneous ambulatory polysomnography in a random sample of 20 subjects, I want to know the level of sensitivity for Actiwatch 2.

Kushida and colleagues found the best accuracy and specificity between Actiwatch and polysomnography when the “high-sensitivity” setting (20 cpm) was used (4). Peterson and colleagues adopted the default sensitivity setting (40 cpm) of Actiwatch and found overestimation of total sleep time and underestimation of wake after sleep onset (5). There is a difference between brain activity and physical movement during sleep, and the discrepancy of sleep parameters between polysomnography and actigraphy is obvious for subjects with insomnia (6). Sitnick and colleagues also described the limitation of actigraphy for detecting night waking (7).

I appreciate the study design by Marcus and colleagues, but methodological validation is important for the evaluation of caffeine therapy for apnea of prematurity and subsequent sleep problems at school age. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

Tomoyuki Kawada, M.D., Ph.D.
Nippon Medical School
Tokyo, Japan

References

1. Marcus CL, Meltzer LJ, Roberts RS, Traylor J, Dix J, D'Ilario J, Asztalos E, Opie G, Doyle LW, Biggs SN, et al. Caffeine for Apnea of Prematurity–Sleep Study. Long-term effects of caffeine therapy for apnea of prematurity on sleep at school age. *Am J Respir Crit Care Med* 2014;190:791–799.
2. Meltzer LJ, Walsh CM, Traylor J, Westin AM. Direct comparison of two new actigraphs and polysomnography in children and adolescents. *Sleep* 2012;35:159–166.
3. Meltzer LJ, Montgomery-Downs HE, Insana SP, Walsh CM. Use of actigraphy for assessment in pediatric sleep research. *Sleep Med Rev* 2012;16:463–475.
4. Kushida CA, Chang A, Gadkary C, Guilleminault C, Carrillo O, Dement WC. Comparison of actigraphic, polysomnographic, and subjective assessment of sleep parameters in sleep-disordered patients. *Sleep Med* 2001;2:389–396.
5. Peterson BT, Chiao P, Pickering E, Freeman J, Zammit GK, Ding Y, Badura LL. Comparison of actigraphy and polysomnography to assess effects of zolpidem in a clinical research unit. *Sleep Med* 2012;13:419–424.
6. Natale V, Léger D, Martoni M, Bayon V, Erbacci A. The role of actigraphy in the assessment of primary insomnia: a retrospective study. *Sleep Med* 2014;15:111–115.
7. Sitnick SL, Goodlin-Jones BL, Anders TF. The use of actigraphy to study sleep disorders in preschoolers: some concerns about detection of nighttime awakenings. *Sleep* 2008;31:395–401.

Copyright © 2014 by the American Thoracic Society

Reply

From the Authors:

Dr. Kawada has raised an important question about the sensitivity setting of the actigraphy used in our study (1). For this study, we chose to use the medium sensitivity threshold.



This decision was based on the findings of Meltzer and colleagues, the only published study to directly compare the Actiwatch 2 (Philips Respironics, Bend, OR) to overnight polysomnography in school-aged children, including those with and without sleep apnea (2). This allowed for the greatest estimate of sensitivity and accuracy. Although the “low” threshold setting would have allowed for greater specificity, this comes at a cost to both sensitivity and accuracy for school-aged children and across levels of sleep-disordered breathing (2).

In general, actigraphy is well known to be highly sensitive to detecting sleep, but rather poor in its specificity or ability to detect wake after sleep onset. In fact, in a review of 228 studies that used actigraphy in pediatric populations, more than half of the validation studies demonstrated a specificity of less than 0.60 (3). This was also true in our study (1).

Dr. Kawada cited several studies that have examined the validity of actigraphy (4–6). However, it should be noted that each of these studies included only adult patients with sleep disorders, including insomnia. Because adults can often lie still for extended periods of time without moving (i.e., motionless wakefulness), actigraphy provides a poor estimate of sleep time in adults. In particular for patients with insomnia, actigraphy will overestimate total sleep time and underestimate wake after sleep onset. Furthermore, the one pediatric study cited by Dr. Kawada included preschoolers (younger than the population we studied) and compared actigraphy to videosomnography rather than overnight polysomnography (7). Not only are additional validation studies needed that compare actigraphy to polysomnography, but it is important for researchers to report all of the relevant settings when using actigraphy (3). ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

Lisa J. Meltzer, Ph.D.
National Jewish Health
Denver, Colorado

Carole L. Marcus, M.B. Ch.B.
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania

References

- Marcus CL, Meltzer LJ, Roberts RS, Traylor J, Dix J, D'Ilario J, Asztalos E, Opie G, Doyle LW, Biggs SN, *et al.*; Caffeine for Apnea of Prematurity–Sleep Study. Long-term effects of caffeine therapy for apnea of prematurity on sleep at school age. *Am J Respir Crit Care Med* 2014;190:791–799.
- Meltzer LJ, Walsh CM, Traylor J, Westin AM. Direct comparison of two new actigraphs and polysomnography in children and adolescents. *Sleep* 2012;35:159–166.
- Meltzer LJ, Montgomery-Downs HE, Insana SP, Walsh CM. Use of actigraphy for assessment in pediatric sleep research. *Sleep Med Rev* 2012;16:463–475.
- Kushida CA, Chang A, Gadkary C, Guilleminault C, Carrillo O, Dement WC. Comparison of actigraphic, polysomnographic, and subjective assessment of sleep parameters in sleep-disordered patients. *Sleep Med* 2001;2:389–396.
- Peterson BT, Chiao P, Pickering E, Freeman J, Zammit GK, Ding Y, Badura LL. Comparison of actigraphy and polysomnography to assess effects of zolpidem in a clinical research unit. *Sleep Med* 2012;13:419–424.
- Natale V, Léger D, Martoni M, Bayon V, Erbacci A. The role of actigraphy in the assessment of primary insomnia: a retrospective study. *Sleep Med* 2014;15:111–115.
- Sitnick SL, Goodlin-Jones BL, Anders TF. The use of actigraphy to study sleep disorders in preschoolers: some concerns about detection of nighttime awakenings. *Sleep* 2008;31:395–401.

Copyright © 2014 by the American Thoracic Society