Comment on Guilleminault C; Lopes C; Hagen CC et al. The cyclic alternating pattern demonstrates increased sleep instability and correlates with fatigue and sleepiness in adults with upper airway resistance syndrome. SLEEP 2007;30(5):639-645

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THE CYCLIC ALTERNATING PATTERN (CAP) IS A WELL DESCRIBED MORPHOLOGICAL FEATURE OF NREM SLEEP, CHARACTERIZED BY PHASIC AMPLITUDE AND FREQUENCY CYCLING OF THE EEG WITH SPECIFIC PERIODIC CHARACTERISTICS.1 PERIODS OF NREM SLEEP WITHOUT CAP ARE LABELED NONCAP. CAP ITSELF CONSISTS OF ACTIVATING “A” PHASES ALTERNATING WITH BASELINE “B” PHASES DEVOID OF THE ABOVE PHASIC ACTIVITY. A1 CAP IS DOMINATED BY SLOW WAVE ACTIVITY AND CONSIDERED TO REFLECT IN PART SLEEP PROMOTING PROCESSES, WHILE A2/A3 CAP HAVE VARIOUS PROPORTIONS OF ALPHA/BETA FREQUENCIES THAT ARE MARKERS OF SLEEP DISRUPTION AND TRANSITIONS. THE LITERATURE GENERALLY SUPPORTS THE ASSERTION THAT AN INCREASE IN CAP RATE (AS A PERCENTAGE OF NREM SLEEP) IS SEEN WITH MANY SLEEP DISRUPTING INFLUENCES, SUCH AS SLEEP APNEA IN ADULTS, RESTLESS LEGS, CHRONIC FATIGUE, CIRCADIAN PHASE MISMATCH, FIBROMYALGIA AND INFLAMMATORY ARTHRITIS, EPILEPSY, AUDITORY STIMULI, DEPRESSION, AND PRIMARY INSOMNIA.2 CONVERSELY, CAP RATE IS REDUCED (AND THUS NON CAP INCREASED) DURING RECOVERY SLEEP FOLLOWING SLEEP DEPRIVATION3 OR POSITIVE AIRWAY PRESSURE TITRATION,4 AND BY SEDATIVE HYPNOTICS (BENZODIAZEPINE AND NON-BENZODIAZEPINE GABA RECEPTOR MODULATORS). A PUBMED SEARCH WITHOUT LIMITS REVEALS BETWEEN 157 AND 97 HITS BASED ON THE EXACT KEYWORDS USED. THE VAST MAJORITY OF STUDIES ARE PURELY DESCRIPTIVE, THERE ARE VIRTUALLY NO ANIMAL MECHANISTIC STUDIES, AND CAP SCORING IS VIRTUALLY NEVER DONE IN CLINICAL PRACTICE. IT IS APPROPRIATE TO ASK IF AFTER MORE THAN 20 YEARS: IS IT WORTH THE EFFORT?

GUILLEMINAULT ET AL IN THIS ISSUE SHOW QUITE CONVINCINGLY THAT INCREASED UPPER AIRWAY RESISTANCE ALONE INDUCES AN INCREASE IN EEG CAP.5 HOWEVER, THEY GO ONE STEP FURTHER BY SHOWING AN ACTUAL CORRELATION OF CAP RATE WITH FATIGUE AND SLEEPINESS IN PATIENTS WITH NON-APEINE, NON-HYPNOSIC SLEEP APNEA. THE FINDING IS IMPORTANT BECAUSE IT SUGGESTS THE FOLLOWING POSSIBILITIES: (1) THERE MAY BE A WAY TO BETTER QUANTIFY THE EFFECT OF INCREASED UPPER AIRWAY RESISTANCE ON SLEEP ELECTROCORTICAL ACTIVITY NOT CAPTURED BY ROUTINE AROUSAL SCORING AND CONVENTIONAL SLEEP STAGES; (2) COMPLETELY NORMALIZING AIRFLOW MAY BE AN OPTIMAL TARGET FOR POSITIVE AIRWAY PRESSURE THERAPY (IF ONE AIM IS TO NORMALIZE EEG PHASIC ACTIVITY); (3) PERIODS OF STABLE FLOW LIMITATION OR OBSTRUCTIVE HYPOVENTILATION MAY ALSO ADVERSELY ALTER CORTICAL ELECTROPHYSIOLOGY; (4) SPECULATIVELY, INDUCING AN INCREASE IN NON-CAP PHARMACOLOGICALLY MAY BENEFIT SOME PATIENTS WITH SLEEP DISORDERED BREATHING SYNDROMES, AS AROUSALS DESTABILIZE SLEEP AND SLEEP-BREATHEING.6

I MAKE A CASE FOR CONSIDERING EEG CAP AS SIMPLY ONE COMPONENT OF AN INTEGRATED STATE APPROACH (STABLE AND UNSTABLE RATHER THAN GRADED) TO NREM SLEEP THAT HAS CHARACTERISTIC BIOLOGICAL FOOTPRINTS IN SEVERAL RECORDABLE PHYSIOLOGICAL TIME SERIES. THESE TIME SERIES INCLUDE THE EEG (POWER AND AMPLITUDE), BLOOD PRESSURE, HEART RATE VARIABILITY (HRV), AUTONOMIC DRIVE BURSTING, RESPIRATION, AND MOTOR ACTIVATION. CORRELATIONS BETWEEN DELTA POWER AND HRV HAVE BEEN DESCRIBED,7 AS HAVE CORRELATIONS BETWEEN HRV AND CAP.8 AN ECG-BASED TECHNIQUE HAS BEEN DESCRIBED THAT GENERATES CARDIOPULMONARY COUPLING SLEEP SPECTROGRAMS UTILIZING HRV AND RESPIRATORY SIGNALS CODED WITHIN R WAVE AMPLITUDE FLUCTUATIONS (THE LATTER IS CALLED THE ECG-DERIVED RESPIRATION SIGNAL). THE TECHNIQUE GENERATES ESTIMATES OF STABLE AND UNSTABLE STATE, WHICH SHOW NO CORRELATION WITH STANDARD STAGES OR DELTA POWER BUT DOES SO WITH CAP AND NON-CAP.9 THE LOW-FREQUENCY CARDIOPULMONARY COUPLING REGIME REFLECTS UNSTABLE NREM SLEEP, CORRELATES WITH EEG CAP, AND LIKE THIS PATTERN, IS SEEN IN HEALTH AND AMPLIFIED BY DISEASE (E.G., SLEEP APNEA). THE HIGH-FREQUENCY CARDIOPULMONARY COUPLING REGIME REFLECTS STABLE STATE IRRESPECTIVE OF CONVENTIONAL STAGE (TYPICALLY STAGE 2 NREM SLEEP), CORRELATES WITH NON-CAP, AND IMPORTANTLY IS ASSOCIATED WITH BLOOD pressure dipping10 AND RESPIRATORY SINUS ARRHYTHMIA. STABLE AND UNSTABLE STATE AS DETECTED BY EEG CAP SCORING OR SLEEP SPECTROGRAMS SHOW SLOWLY SWITCHING INDEPENDENT OF REM/NREM CYCLES. SIMILARLY, SLOW MAY ALSO BE STABLE OR UNSTABLE — IN THE LATTER CASE CHARACTERIZED BY MICROINTRUSIONS OF SLEEP INTO WAKE STATE. UNUSUALLY RAPID BIOLOGICAL PROGRESS FROM STABLE WAKE TO SLEEP WOULD NEED LARGE INCREASES IN SLEEP DRIVE, WHILE MILD TO MODERATE AROUSING STIMULI WOULD INCREASE LOW-FREQUENCY OSCILLATIONS (USUALLY A PERIOD OF 30-60 SECONDS, NOT THE SAME AS THE LOW-FREQUENCY SPECTRUM OF HRV) OF THE EEG, AND INDUCE CYCLIC VARIATIONS IN HEART RATE, AUTONOMIC DRIVE, AND TIDAL VOLUME, ENTRAINED TO THE SAME LOW FREQUENCY. TO MOVE RAPIDLY FROM STABLE SLEEP TO WAKE WOULD NEED POWERFUL AROUSING STIMULI (E.G., FIRE ALARM) AND MAY BE INCOMPLETE (E.G., NIGHT TERROR). REM SLEEP MAY ALSO BE CONSIDERED IN THE DOMAIN OF STABILITY — UNSTABLE REM SLEEP HAS INTERMITTENT INTRUSIONS OF NREM SLEEP OR WAKE. NARCOLEPTICS HAVE BEEN REPORTED TO HAVE REDUCED CAP RATES, PERHAPS A MARKER OF REDUCED ENDOGENOUS AROUSING INFLUENCES.

Is scoring CAP practical? Manual approaches are slow (adding

Disclosure Statement

Dr. Thomas is a consultant to Total Sleep Holdings a sleep laboratory services company and is named on a patent submitted for a method to use low concentration carbon dioxide to treat central and complex sleep apnea and a patent submitted for a method to determine sleep stability from ECG using cardiopulmonary coupling estimates.

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further costs to clinical studies), tedious, and often a labor of love for an individual study. The scoring rules are complicated, and created to “fit” the visual pattern, rather than based on specific biological processes. For example, the 30% amplitude criterion for CAP A1 phases is as arbitrary, as the 75 microvolt criterion we all know so well. The criteria are a “one size fits all” approach, although individual authors have made modifications for the pediatric population. Automated approaches are off by about 30% at least, and need careful manual correction; moreover as computer programs tend to do, numerous “statistics” of dubious value are generated. The CAP pattern is actually quite easy to recognize (vs. scoring) by compressing the digital polysomnography screen to 60-120 seconds. While CAP is an EEG pattern, it is usually obvious in sleep apnea syndromes that heart rate, respiration, motor activation, oximetry, and blood pressure are all oscillating together, biologically “coupled” and entrained. Thus, in those under conditions of simulated high altitude, the CAP cycle time is 20-25 seconds, while in heart failure with periodic breathing, the CAP cycle time is 60+ seconds (unpublished observations). The <1 Hz slow oscillation is the fundamental building block

Figure 1—Beyond EEG Cyclic Alternating Pattern. Healthy 23-year-old female without clinical sleep disorders symptoms or polysomnographic sleep disordered breathing. The figure shows (in each part of the figure, from top) the standard sleep EEG (C4-A1), the same channel with a 1 Hz high-frequency EEG filter, electrocardiogram (ECG), nasal flow with a cannula-pressure transducer system, and respiratory effort (chest) with piezo bands. The filter allows appreciation of the <1 Hz slow oscillation. In the top half of the figure, standard NREM stage is 4, EEG stability type is non-CAP, sinus arrhythmia is clearly evident on the ECG, the ECG shows amplitude fluctuation on a breath to breath basis (ECG-derived respiration), the slow oscillation has a “continuous mode,” and the sleep spectrogram showed high frequency coupling (not shown). In the lower half of the figure, standard NREM stage is 2, EEG stability type is CAP, the ECG shows subtle acceleration in relation to the K complexes, the slow oscillation has a “discontinuous mode,” and the sleep spectrogram showed low frequency coupling (not shown). Thus, evaluating coupling between multiple biological signals may provide insights not evident by sole focus on a single type of signal.
of NREM sleep; A1 CAP and non-CAP are especially enriched with this frequency. A2 and A3 CAP are associated with inhibition of the slow oscillation (Figure 1). As the slow oscillation may be obtained “vertically” in the brain from subcortical and limbic sites, organizes numerous important electrocortical rhythms such as spindles, and modulates calcium entry into cortical synapses, the proportions of CAP vs. non-CAP and A1 vs. A2/A3 may be important markers of sleep quality that have a clearer biological basis than standard stages. This is an area that deserves study.

Is CAP useful in clinical practice at the level of the individual patient? Non-CAP dominates rebound effects during positive airway pressure titration, and can provide a false sense of therapeutic efficacy; actual scoring is not necessary for this purpose; recognizing stable and unstable state is enough. Persistence of an elevated CAP rate with treatment (in sleep apnea, depression, insomnia, restless legs) could be a marker of suboptimal biological efficacy. However, besides outcome and mechanistic studies, for practical clinical utilization one or more of the following is required:

1. An automated EEG method that works without fuss, perhaps by using learning algorithms; simplification of the scoring system may be in order.
2. Understanding the implications of similarities and differences of what is scored as “CAP” in adults and children.
3. Use of methods independent of the EEG that may also usefully complement assessment of stable and unstable sleep states.

REFERENCES: