

## MECHANISM OF BIOFEEDBACK THERAPY FOR URGENCY INCONTINENCE

### 1. Hypothesis / Aims of study

After >50 years of investigation, the relationship between “non-neurogenic” urgency incontinence (UI) and its assumed cause, detrusor overactivity (DO), remains unclear, and both etiology and the mechanisms underlying therapeutic response remain unknown. To gain further insight, we enrolled older adults with UI in a prospective, clinical-urodynamic investigation. The goal was to identify the key physiological parameters that predict and/or likely mediate response to a widely recommended behavioral therapy (biofeedback-assisted pelvic floor muscle training, BFB).

### 2. Study design, materials and methods

Subjects were cognitively and functionally intact, community-dwelling women aged  $\geq 60$  years with at least 2 UI episodes per week. All underwent detailed clinical evaluation, including history, physical exam, lab tests, and review of old records; 3-day bladder diary; 24-hour pad test; and comprehensive videourodynamics with simultaneous videocystosphincterometry, urethral testing, and pressure/flow study. A standard protocol was used to elicit DO if it did not appear spontaneously. Each evaluation was performed before and after therapy. EMG-based BFB followed a standard published protocol [1] and included 4 clinic visits and home practice. Therapeutic response was defined *a priori* and based on bladder diary and reassessed based on 24-hour pad test. Since pad test results were comparable with those based on the bladder diary, only the latter are presented. The study was funded by NIH.

**Predictors** were defined as parameters whose *baseline values* correlated with therapeutic response. **Mediators** were defined as parameters whose *change* from baseline (1) correlated with response and (2) was in a direction and of a magnitude sufficient to be both statistically significant and biologically plausible. The latter safeguard was employed to distinguish epiphenomena from changes that likely play a key role in mediating response. As a further safeguard, candidate physiological parameters were selected *a priori*. In addition, to enhance statistical power, parameters were grouped *a priori* into 5 physiological domains (bladder proprioception, capacity, contractility, DO characteristics [briskness and amplitude], and sphincter adequacy), with 7 possible confounding variables selected as well.

### 3. Results

Of 649 subjects screened, 279 enrolled, and 183 (60-93 years, mean=74) completed the 8 week study; 96 were ineligible on urodynamics or withdrew for logistical reasons. Overall, BFB reduced the mean frequency of UI from 3.6 to 2.0 episodes per 24 h and the weight of urine lost from 99 g to 55 g per 24 h. The percentage of responders (defined as  $\geq 50\%$  reduction in incontinence frequency) was 55%. 13% of subjects were completely dry on the end-study 3-day bladder diary.

Baseline UI frequency was a significant confounding predictor ( $P = 0.04$ ). With less than one UI episode/day the chance of becoming completely dry after BFB was 35%, but for more frequent UI it was 17% or less (depending on the frequency). For this reason the prediction/ mediation results were controlled for baseline UI frequency. Only one other potential confounder was significant: 24-h voiding frequency decreased in responders but not in non-responders, suggesting that it was a result of improvement rather than a confounder. Age did not affect results

Only 4 urodynamic variables were significant **predictors** of response to BFB. These comprised 4 domains: proprioception ( $P = 0.05$ ), DO characteristics (briskness and amplitude,  $P = 0.005$  for each), sphincter adequacy ( $P = 0.05$ ), and detrusor contractility ( $P = 0.03$ ). Only 2 parameters were statistically significant in the **mediators** analysis (both of the DO characteristics,  $P = 0.01-0.04$ ); proprioception just missed ( $p=0.06$ ).

Despite extensive provocation, DO was observed in only 43% of subjects during baseline urodynamics. Characteristics of DO could be measured only in this subgroup, but high DO velocity (briskness) and high amplitude (pressure) predicted poorer outcome. The actual presence of DO was not a significant predictor of response (51% of those with baseline DO responded vs. 58% of those without DO,  $p=0.3$ ). However, DO was a mediator: among subjects whose DO could be elicited at baseline, it remained elicitable after therapy in 78% of non-responders but in only 54% of responders ( $P = 0.03$ ).

### 4. Interpretation of results

This study confirms the efficacy of BFB, especially for those with less frequent UI at baseline, and this information may be helpful for patient counseling. The study also confirms that urodynamic changes can be detected among those who respond to BFB: first desire occurs at higher volumes ( $p=0.06$ ). DO becomes less elicitable and, if DO can be elicited, its briskness and amplitude decline among responders. Associated with these changes, voiding becomes less frequent, reflecting less need for pre-emptive voiding.

Except for DO, however, the identified urodynamic changes were few and unimpressive despite their statistical significance. For example, proprioception was altered among responders and in the direction postulated, but statistical significance was observed for only one of seven measures of it and the measure that was significant as a predictor differed from the one that was significant as a potential mediator. Thus, changes in bladder proprioception may not play a major role in response to BFB. A similar argument applies to sphincter adequacy and detrusor contractility. By contrast, DO does appear to play an important role. Successful BFB seems to work by making DO more difficult to elicit. DO characteristics are also predictive: BFB works less well for incontinence associated with more aggressive (brisk, high-amplitude) DO, suggesting that there are more aggressive

and less aggressive phenotypes with different responses to treatment. Unfortunately, aggressiveness can only be determined by invasive testing and in a minority of patients and so this information is less helpful in selecting appropriate treatment.

## 5. Concluding message

BFB improves urgency incontinence in older women, especially among those with less severe incontinence. The effectiveness of BFB probably involves multiple domains, in particular DO characteristics. BFB is more effective for less aggressive DO and seems to work primarily by reducing the elicibility of DO, probably reflecting BFB training to reinforce coping methods that improve control of continence and voiding.

## References

1. Burgio KL, Locher JL, et al: Behavioral vs drug treatment for urge urinary incontinence in older women: a randomized controlled trial. JAMA. 1998;280(23):1995-2000

<b><i>Specify source of funding or grant</i></b>	<b>NIH 5RO1AG020629-02</b>
<b><i>Is this a clinical trial?</i></b>	<b>Yes</b>
<b><i>Is this study registered in a public clinical trials registry?</i></b>	<b>Yes</b>
<b><i>Specify Name of Public Registry, Registration Number</i></b>	<b>clinicaltrials.gov NCT00177541</b>
<b><i>Is this a Randomised Controlled Trial (RCT)?</i></b>	<b>No</b>
<b><i>What were the subjects in the study?</i></b>	<b>HUMAN</b>
<b><i>Was this study approved by an ethics committee?</i></b>	<b>Yes</b>
<b><i>Specify Name of Ethics Committee</i></b>	<b>IRB University of Pittsburgh</b>
<b><i>Was the Declaration of Helsinki followed?</i></b>	<b>Yes</b>
<b><i>Was informed consent obtained from the patients?</i></b>	<b>Yes</b>