Specific Aims: Overactive bladder (**OAB**)[1-3] is a chronic filling-phase condition that affects nearly 20% of the population[4]. Despite this high prevalence, there is limited understanding of OAB pathophysiology. A critical barrier in the understanding of OAB is the lack of an objective method to sub-categorize different forms of this disorder. Furthermore, during cystometrics testing, the gold standard for the evaluation of voiding dysfunction, pressure generally increases little during bladder filling and does not reflect detrusor wall tension[5]. It is therefore not surprising that level I evidence now exists showing that human cystometrics are often unreliable and may provide no benefit over a limited office-based physical exam in the management of several forms of voiding dysfunction[6]. Because increased detrusor wall tension is thought to be a key factor in OAB pathophysiology[7-9], true filling phase physiology cannot be evaluated during standard clinical cystometrics. Thus, there is a pressing need to develop mechanistically relevant cystometric tests that utilize detrusor wall tension to objectively sub-categorize OAB**.**

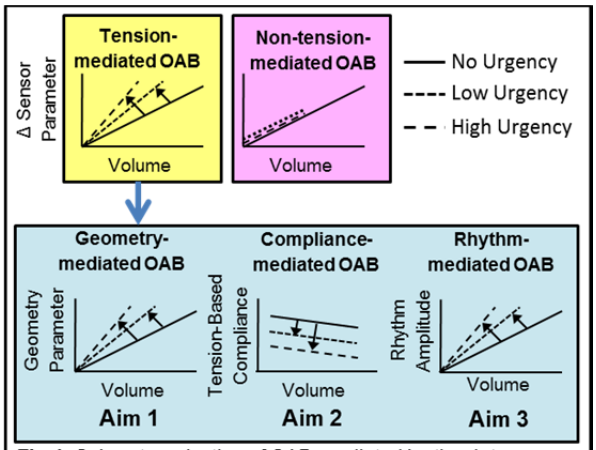

Fig 1. Sub-categorization of OAB predicted by the detrusor tension sensor model (**see Fig 2**).

Based on our preclinical work, we have developed a tension sensor model (**see fig 2**) and have identified three mechanical properties that can directly affect detrusor wall tension and can be used to objectively sub-categorize OAB: **bladder geometry**, **dynamic compliance**, and **spontaneous rhythmic contractions (SRC)**. **Bladder geometry**: According to the Law of Laplace, where tension is proportional to pressure x radius, alterations in filling bladder geometry induced by external compressive forces (i.e. constipation or obesity), can create localized areas of increased tension due purely to radius changes (filling geometry) without pressure changes. Yet, readily available non-invasive imaging modalities, such as ultrasound, have not been used to assess bladder geometry during clinical cystometrics. **Dynamic Compliance**: We have also shown that detrusor compliance is not static but can be acutely regulated depending on strain-history (passive stretches) and activation history (active contractions)[10-16], a term we now call "dynamic compliance." We and others have established that passive changes that lengthen the detrusor muscle, increase dynamic compliance (decrease wall tension) likely through breakage of cycling cross-bridges[10,11,13]. Additionally, we have demonstrated that dynamic compliance is altered in an animal model of detrusor overactivity[16]. **SRC**: We have also found that detrusor wall tension can be affected by SRC[10] that are commonly identified in mammalian bladders during filling[17,18] and others have shown that elevated SRC may be linked to OAB[7,19].

Importantly, current cystometrics do not evaluate bladder geometry, dynamic compliance, or SRC. Based on this knowledge, our multi-PI team of a neuro-urologist and a mechanical engineer propose to develop a novel cystometric evaluation system to identify and objectively characterize three new subsets of tension-mediated OAB diagnosed by alterations in 1) bladder geometry, 2) dynamic compliance, and 3) SRC (**Fig 1, Blue Box**). The system will provide an objective method to separate OAB that derives directly from alterations in detrusor wall tension (**Fig 1, Yellow Box**) from a 4th subset of non-tension-mediated OAB that derives from alterations in nervous system processing (**Fig 1, Pink Box**) as we have previously shown the profound impact of psychiatric comorbidities on voiding dysfunction[20,21]. The system will be validated in human subjects with varying degrees of OAB severity (no urgency, low urgency, and high urgency) during extended cystometric studies. In doing so, we expect to redefine clinical cystometrics and identify novel biomechanical mechanisms for the improved diagnosis and treatment of OAB. We will accomplish this goal in 3 aims as follows:

Aim 1. Develop a novel cystometric test to identify and objectively characterize an OAB subset mediated by altered bladder geometry (perimeter, shape, and surface area).

Aim 2. Develop a novel cystometric test to identify and objectively characterize an OAB subset mediated by altered dynamic compliance (strain-history and activation-history dependent compliance).

Aim 3. Develop a novel cystometric test to identify and objectively characterize an OAB subset mediated by altered SRC (rhythmic pressure fluctuations).

Our new filling phase cystometrics includes 1) a sliding scale Urgency Meter to continuously record patient-reported ***acute*** urgency, 2) two and three dimensional bladder ultrasound used to provide real-time anatomic measurements to determine the effect of geometry and used for dynamic compliance calculations, and 3) Fast Fourier Transform (**FFT**) analysis to objectively measure SRC. These new metrics will provide a quantitative mechanistic link to identify and objectively characterize four new subsets of OAB. Furthermore, these new metrics may lead to more targeted treatments for OAB and identify novel mechanisms for future therapies.