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VARIABILITY IN THE SPONTANEOUS CONTRACTILITY PROFILE OF THE HUMAN PROSTATE GLAND: IMPLICATIONS FOR A PERSONALIZED TREATMENT APPROACH TO BETTER MANAGE BPH

Hypothesis / aims of study

A greater insight into human spontaneous prostatic contractions is fundamental to understanding a) the pathophysiology of benign prostatic hyperplasia (BPH) and b) the mechanism of action of current pharmacotherapies that target prostatic smooth muscle tone and hence improve the lower urinary tract symptoms (LUTS) associated with BPH. However, a clear limitation with recent studies on contractility within the human prostate gland includes the lack of acquisition of patients' data. In this study, we demonstrate that there are individual differences in the spontaneous contractile profile recorded in the transition zone in fresh prostatic specimens from 34 men, where individual responses to current pharmacotherapies also differ. For the first time, we can demonstrate that the variability in patients' responses to clinically used drugs can be directly correlated with patient characteristics.

Study design, materials and methods

Transition zone tissue (10mm X 15mm) from the prostate gland was obtained from consenting patients undergoing radical prostatectomy. Contractile recordings were made from prostatic preparations (5mm X 10mm) using standard tension recording techniques as we have previously described. A paired Student's t-test was used to test for statistical significance ($P < 0.05$).

Results

In all 34 specimens, robust spontaneous contractions were recorded at a frequency of 1.92 +/- 0.14 contractions per minute and an average duration of 13.2 +/- 1.2 seconds per contraction. The basal tension was 4.58 +/- 0.23 mN and the amplitude of each contraction was 0.23 +/- 0.02 N/g. Overall, the PDE5 inhibitor, sildenafil [10-5M] significantly ($p< 0.05$, $n= 12$) decreased the basal tension and frequency of spontaneous contractions within the transition zone specimens. However, there was notable interpatient variability, with a subset of patients unresponsive to sildenafil. Regression analysis determined that age was significantly ($R2= 0.448$, $p< 0.05$) negatively correlated with responsiveness to sildenafil, with younger men having a greater reduction in the frequency of spontaneous contractility. In contrast, older men responded better to the current gold standard pharmacological agent, tamsulosin ($R2= 0.362$, $p< 0.05$).

Interpretation of results

This study demonstrates limitations with pooling data, as the varying parameters measured in the contractility profiles of the different patients exhibited inherent variability. For example, the basal tension in the transition zone within the prostate gland ranged from 1.46 mN to 7.32 mN in specimens from different patients. Similarly, the amplitude of spontaneous contractions in the transition zone ranged from 0.11 $N.g^{-1}$ to 0.74 $N.g^{-1}$ and the frequency ranged from 0.82 min^{-1} to 4.57 min^{-1}. The inherent variability is also mirrored in the immunohistochemistry results where staining for smooth muscle actin in the TZ, differed considerably across 5 patients. Furthermore, our study indicates that interpatient variability to pharmacotherapies such as sildenafil and tamsulosin in an *in vitro* model can be correlated with clinical parameters.

Concluding message

Consideration of individual patient's clinical data may explain the varying parameters measured in the contractility profiles of different patients in this study. In addition, this study is the first to demonstrate that pharmacotherapies that have a direct modulatory effect on human prostatic smooth muscle tone in some patients, may not modulate the contractility of others. Such information may lead to the development of a more personalised treatment approach to better manage the symptoms associated with BPH, in addition to improving the quality of life for patients.

Disclosures

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