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Estimation of bladder contractility from intravesical pressure-volume measurements.

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Short title. Measurement of bladder contractility
Abstract

Aim. To describe parameters from urodynamic pressure recordings that describe urinary bladder contractility through the use of principles of muscle mechanics.

Methods. Subtracted detrusor pressure and voided flow were recorded from patients undergoing filling cystometry. The isovolumetric increase of detrusor pressure, \( p \), of a voluntary bladder contraction before voiding was used to generate a plot of \( (dp/dt)/p \) vs \( p \). Extrapolation of the plot to the y-axis and the x-axis generated a contractility parameter, \( v_{CE} \), (the maximum rate of pressure development) and the maximum isovolumetric pressure, \( p_0 \), respectively. Similar curves were obtained in ex vivo pig bladders with different concentrations of the inotropic agent carbachol and shown in a supplement.

Results. Values of \( v_{CE} \), but not \( p_0 \), diminished with age in female subjects. \( v_{CE} \) was most significantly associated with the 20-80% duration of isovolumetric contraction \( t_{20-80} \); and a weaker association with maximum flow rate and BCI in women. \( p_0 \) was not associated with any urodynamic variable in women, but in men was with \( t_{20-80} \) and isovolumetric pressure indices.

Conclusions. The rate of isovolumetric subtracted detrusor pressure \( (t_{20-80}) \) increase shows a very significant association with indices of bladder contractility as derived from a derived force-velocity curve. We propose that \( t_{20-80} \) is a detrusor contractility parameter (DCP).
Introduction

To void completely the bladder must generate sufficient intravesical pressure to overcome outflow tract resistance and sustain this to allow complete voiding. However, the bladder may generate excessively large pressures that can impact on upper tract integrity or may exhibit an underactive phenotype, resulting in incomplete bladder emptying. There is a clinical need to identify the causes of abnormal voiding to allow proper management of these conditions and identify people at risk if being considered for surgery to improve voiding. In particular, men who require relief from voiding lower urinary tract symptoms (LUTS) may not benefit from surgery if impaired bladder contractility is the cause. Likewise, women may be at risk of voiding difficulty after surgery to treat stress urinary incontinence, even if there were no prior voiding LUTS.

A rise of detrusor pressure results from increased bladder wall tension generated by contracting detrusor smooth muscle. However, several lower urinary tract properties contribute to voiding: the magnitude of urethral resistance; the strength and duration of detrusor smooth muscle contraction; and initial bladder volume which by Laplace's Law is an inverse function of detrusor pressure. Of fundamental interest is whether or not impaired or enhanced detrusor muscle contractile function contributes to abnormal voiding. Several urodynamic-based definitions of bladder contractility have been defined, e.g. a bladder contractility index (BCI)², Watts factor³ and bladder outlet relation,⁴ but these are also influenced by outflow tract properties. Furthermore, such parameters are poorly validated in women. Therefore, it is desirable to define a gender-neutral urodynamic-based parameter that reflects physiological bladder contractility.
Smooth and cardiac muscle exhibit a property that contractile strength depends not only on resting fibre length but also on an intrinsic inotropic state. The latter is an alteration of contractile performance independent of resting length and physiologically is defined as a change of contractility: this term therefore has a specific meaning for isometric (muscle tension developed at constant length) or isotonic (muscle shortening at constant load) contractions. Changes of contractility have been demonstrated in the intact heart and isolated cardiac preparations \(^5\)-\(^7\) and evaluated in the bladder.\(^8\),\(^9\) To identify patients with reduced cardiac contractility (heart failure), it was important to identify parameters independent of preload and afterload, as these affect muscle fibre length and contractile strength.\(^5\) The usefulness of indices derived from the rise of isovolumetric ventricular pressure \((P)\) in the cardiac cycle to define cardiac contractility is validated, especially from a plot of \((dP/dt).P\) as a function of \(P\) itself.\(^10\),\(^11\) These indices are the extrapolated fits of this relation to: a) the \(y\)-axis \((dP/dt).P\)-axis) which represents maximum velocity of muscle shortening, \(v_{CE}\); b) the \(x\)-axis \((P\)-axis) which represents maximum isovolumetric pressure, \(P_0\). The indices reflect the action of positive and negative inotropic agents and thus changes to cardiac contractility. However, this analysis has not been applied to smooth muscle-lined organs. We used urodynamic recordings of bladder contractile function to obtain a practical measure of true bladder contractility based on the above cardiac principles and how this may be used to understand different disorders of bladder function.
Materials and Methods

Data collection. Anonymised data were obtained from 49 patients attending the urodynamic clinic at Southmead Hospital, North Bristol NHS Trust. Inclusion criteria were patients listed for routine or video urodynamics and with voided volumes greater than 100 ml. Pressure readings on both abdominal and intravesical lines were obtained following ICS guidelines.\textsuperscript{12} Exclusion criteria were: evidence of a bladder diverticulum which would prevent a constant-volume contraction (four); voiding achieved mainly with additional abdominal straining (five), leaving 40 records (21 male, 19 female patients) for analysis. Data were anonymised and collected according to standard departmental protocols as part of urodynamic testing. Ethical approval was obtained from the regional research ethics committee.

Urodynamic measurements in subjects. Subjects emptied their bladder before urodynamics. An Aquarius urodynamics system (Laborie; Mississauga, Canada) used water-filled catheters to record infused volume as a function of time and values of abdominal and intravesical pressures to obtain calculated detrusor pressure, $P_{\text{det}}$, in accordance with ICS Good Urodynamics Practices.\textsuperscript{12} Flow during voiding was measured directly. Analogue measurements were digitised at 50 kHz and stored on the urodynamics system computer. For all other aspects, the manufacturer’s default values were used for data acquisition, namely 0.8 seconds delay time added to the pressure trace to align it with the flow-meter recording. Data were retrieved from these files at 0.05 kHz for subsequent analysis. Figure 1A, B shows the different measurements made from urodynamic recordings. Derived indices were: the maximum rate of $P_{\text{det}}$ change during isovolumetric contraction, $dP_{\text{det}}/dt_{\text{max}}$; isovolumetric contraction duration from 20\% to 80\% $\Delta P_{\text{sv}}$ ($t_{80-20}$); bladder contractility index (BCI; $P_{\text{det}}Q_{\text{max}}+5Q_{\text{max}}$) and bladder outflow obstruction index (BOOI; $P_{\text{det}}Q_{\text{max}}−2Q_{\text{max}}$).
Smoothing pressure traces. $P_{\text{det}}$ measurements were made during isovolumetric bladder contractions, between the onset of a rise of detrusor pressure and the beginning of flow, $Q$ (Figure 2A). The base-line (pre-contraction) value of $P_{\text{det}}$ was subtracted from values during contraction, henceforth called $P$. The dependent variable in the final analysis, $(dP/dt)/P^1$ – see supplementary material - is significantly influenced by artifactual pressure fluctuations and $P$-data were smoothed by calculating running averages ($RA$), equation 1, with $n=10, 20, 50$ or $100$, i.e. averaging occurred over $0.2, 0.4, 1.0$ or $2.0$ s:

$$RA_n = (x_1+x_2+...+x_n)/n, \quad RA_{n+1} = (x_2+x_3+...+x_{n+1})/n, \quad RA_{n+2} = (x_3+x_4+...+x_{n+2})/n, \ldots$$  \hspace{1cm} 1

In this analysis a value of $n=20$ was used, i.e. a value of $0.4$ s running average time was chosen that imposed only a $2\%$ slowing of the pressure trace.

Data analysis. The supplementary data describe the rationale for estimating a contractility parameter of an isovolumetrically-contracting spheroid organ. A plot of $(dP/dt).P^{-1}$ vs $P$ yields a phase loop of which the declining portion at higher $P$-values is described by a hyperbolic function that intercepts the $y$-axis (i.e. at $P=0$) to yield a value for the maximum velocity of contractile element shortening ($v_{\text{CE}}$). An increase of $v_{\text{CE}}$ is interpreted as enhanced bladder contractility. The intercept on the $x$-axis is the maximal isovolumetric pressure, $P_0$, that would have been achieved had the outflow tract not opened. A value of bladder wall tension, $T_0$, was calculated from the Laplace equation: $T_0 = P_0/r/2$; where $r$ is bladder radius, calculated from the filling volume, $V$, at initiation of voiding: i.e. $r = \sqrt[3]{\frac{0.75V}{\pi}}$. Values of $v_{\text{CE}}$ and $P_0$ were compared to indices as measured or calculated from urodynamic traces (Figure 1) to determine where the best associations were observed. For isolated pig bladders data values of $v_{\text{CE}}$ and $P_0$ were plotted as a function of the carbachol concentration.
Data presentation and statistical analyses. Group values are represented as medians (25, 75% interquartiles). Associations between variables were calculated from a Spearman's correlation coefficient, $\rho$, whose significance was tested by calculation of a $t$-value from $\rho$ using $t = \rho \sqrt{\frac{n-2}{1-\rho^2}}$, with subsequent estimation of $p$-values. Differences between sets were tested by ANOVA, with post hoc Bonferroni multiple comparisons. In total, 10 (see Results) separate hypotheses were tested for a significant association between $v_{CE}$ or $P_0$ and a particular urodynamic variable. To minimise the chance of a spurious level of significance arising from these multiple tests the $p$-value for significance was reduced from one of $p<0.05$ by a correction to $p<0.005$ (i.e. $p<0.05/10$). A least-squares iterative fitting program (KaleidaGraph, Synergy Inc) was used to fit linear and non-linear functions to data sets.
Results

Patient urodynamic characteristics and contractility indices. Table I shows urodynamic-derived values of lower urinary tract function (figure 1). All variables were similar in males and females, except: in females calculated BOOI was smaller. Values of the contractility indices $v_{CE}$ and $P_0$, as well as calculated $T_0$, are also shown in table 1 and were also similar in males and females.

Smoothing of pressure waveforms. Figure 2A shows an example of the rise of subtracted detrusor pressure in the isovolumetric phase for an unsmoothed ($P$) trace and smoothed $n=10, 20, 50$ or $100$ (eq 1, Methods) i.e. averaging over 0.2, 0.4, 1.0 or 2.0 s for data recorded at 0.05 kHz. Traces are shown as $P$, $P_{10}$, $P_{20}$, $P_{50}$ and $P_{100}$. The extent of time delay is shown in Figure 2B where values of $P$ are plotted against $P_n$. For no introduced time-delay the slope of the line would be unity. From 28 sample traces the slopes were 1.007 [0.999, 1.104], 1.020 [1.000, 1.033], 1.044 [1.007, 1.083] for averaging over 0.2 ($n=10$), 0.4 ($n=20$), 1.0 ($n=50$) and 2.0 ($n=100$) s, respectively. Heuristically a value of $n=20$ was chosen for onward analysis, which would introduce an error of 2% [0.0 – 3.3%] in traces and consequent derived values of $v_{CE}$.

Relation of $v_{CE}$ to urodynamic variables. $v_{CE}$ values were negatively associated with age for females ($p=0.03; n=19; 22$-85 years) but not for males ($n=21; 22$-84 years) subjects. For urodynamic variables there were significant negative associations for female and male subjects with $t_{20-80}$ ($p=0.000002$ and 0.002, respectively; $r=-0.636$ and -0.861). Positive associations for females only were also shown for $Q_{max}$ and BCI (both $p=0.002; r=0.668$ and 0.663, respectively). There were no significant associations for other urodynamic variables, i.e. $\Delta P_{det}$, $P_{detQ_{init}}$, $\Delta P_{isv}$, $P_{detQ_{max}}$, $P_{det}$ time or $Q$ time, nor the calculated index BOOI for either
gender. Figure 3A-D shows the relationships between $v_{CE}$ and age, $t_{20-80}$, $Q_{max}$ or BCI for female and male subjects.

Relation of $P_0$ to urodynamic variables. There was no association of $P_0$ with age for subjects of either gender. A different pattern of associations was observed for $P_0$ with urodynamic variables compared to $v_{CE}$. For female subjects no urodynamic variable showed a significant relationship with $P_0$. For male subjects $P_0$ was positively associated with $\Delta P_{det}$, $P_{det Q_{init}}$, $P_{det Q_{max}}$, and $P_{det Q_{max}}$ (all $p<0.00001$; $r=0.893, 0.839, 0.917, 0.816$ respectively). $P_0$ was also negatively associated with $t_{20-80}$ ($p=0.005; r=-0.694$) and BOOI ($p<0.0001; r=-0.751$), but not for $P_{det time}$, $Q_{max}$, $Q_{time}$ nor BCI. Figure 3E shows the association between $P_0$ and $\Delta P_{ISV}$.
Description of bladder contractility. Transformation of the isovolumetric contraction phase allows calculation of bladder wall contractility from pressure urodynamic traces in patients. Key to the analysis is estimation of muscle contractility from the intercept of a force-velocity curve with the y-axis, $v_{CE}$, which represents the maximum, unloaded velocity of shortening.

Developed for tension measurements in skeletal muscle, the analysis of $v_{CE}$ was then applied to cardiac and smooth muscle preparations. Its verification in isolated smooth muscle cells further demonstrated that the relationship is a general feature of muscle cells. $v_{CE}$ is related to crossbridge turnover and myosin ATPase muscle activity, and positive inotropic interventions increase the value. The principle of generating force-velocity curves was extrapolated to isovolumetric hollow organs such as the heart, where pressure is proportional to tangential wall tension, and it was shown that addition of myocardial inotropic agents altered $v_{CE}$ values in a consistent manner. The method therefore generates a contractility index that derives from changes to the speed of contraction of the bladder wall.

We have shown that force-velocity curves may also be generated from isovolumetric phases of voiding bladder contractions, and validated the approach in pig bladders (see supplement), showing that an inotropic agent, carbachol, altered $v_{CE}$. Moreover, comparison of $v_{CE}$ values with urodynamic variables showed that the strongest association was with time-dependent variables of the isovolumetric rise of pressure, before voiding begins, i.e. the time from 20-80% ($t_{20-80}$) of this phase. We propose this interval is a superior measure of bladder contractility as derived from urodynamic traces. Moreover, this association was independent of gender, unlike the case for urodynamic variables such as BCI, which is verified only for men. A parallel increase of maximum isovolumetric pressure, $P_0$, and contractility would be anticipated in an isovolumetric system but not in a voiding bladder, as in the latter the energy...
of contraction would also be dissipated in causing urine flow at the expense of a continuous rise of pressure. Data from an isolated, arterially perfused pig bladder validated the approach by showing that addition of a contractile agonist, carbachol in rising concentrations, increased \( v_{CE} \), as well as both the maximum rate of increase of pressure and maximum pressure itself.

Although there was a significant association between \( v_{CE} \) and \( P_0 \) in the human bladder these two derived variables measure different aspects of bladder function. Values of \( v_{CE} \), reflecting different states of contractility and with units of reciprocal time, were strongly associated with the time course of the increase of isovolumetric pressure, as may be expected, but not with any urodynamic pressure parameter. \( P_0 \) is a measure of steady-state tension and is determined also by the number of muscle fibres recruited to enable a detrusor contraction, as well as the contractility of individual muscle fibres. \( P_0 \) showed stronger associations with pressure urodynamic indices than with time-dependent indices of isovolumetric pressure and is a less reliable estimation of detrusor muscle contractility itself.

Gender differences. There were no gender differences in \( v_{CE} \) or \( P_0 \), nor in individual urodynamic variables, except BOOI: table 1. However, there were striking differences between associations of \( v_{CE} \) or \( P_0 \) with urodynamic variables. For \( v_{CE} \) values, an age-dependent decline was present in females but not males, suggesting a decline of detrusor contractility with age in women. There was also a significant association of \( v_{CE} \) with \( Q_{max} \), and its derived variable BCI, in females but not males: thus in males factors other than muscle contractility, e.g. outflow tract resistance, influence the rate of urine flow.

Limitations to the generation of force-velocity curves in an isovolumetric bladder. i) Pressure in a hollow organ is proportional to tangential wall tension if it is truly isovolumetric and wall
thickness is unchanging during contraction.\textsuperscript{16} Thus, patients with evident bladder diverticula should be excluded from the analysis, as chamber volume would change during these otherwise isovolumetric contractions. ii) In principle, contractility estimates are based on changes to muscle or wall tension. In different patients, bladder volume during isovolumetric contraction was not very variable and the relationship between $\Delta P_{\text{ISV}}$ and calculated wall tension was very significant ($\rho=0.987$, $n=40$, $p<0.000001$). Thus, changes of isovolumetric pressure during voiding are proportional to those of wall tension. iii) The absolute value of the force-velocity curve intercept with the $y$-axis to estimate $v_{CE}$ also depends on wall stiffness, $k$, and it was assumed to be unchanging during the contraction. iv) The urodynamic system that was used imposes an in-built delay of 0.8 s between the pressure and flow values, so that this final period of the isovolumetric pressure curve would be unreliable for analysis and was therefore not used. v) All analyses were performed on voluntary contractions - it will be of further interest to also analyse involuntary detrusor contractions.

Conclusions. The maximum velocity of an unloaded detrusor contraction, $v_{CE}$, shows a very close association with the urodynamic 20-80\% time of the isovolumetric pressure contraction, $t_{20-80}$, we propose calling the detrusor contractility parameter (DCM). $v_{CE}$ is an index of muscle contractility as verified in parallel pig bladders experiments. This method offers considerable advantages over current urodynamic estimates of contractility such as BCI, which is a flow- and volume-dependent variable and verified only for men. Its measurement can contribute to the debate regarding the concept of bladder underactivity as a true decline of bladder contractile function, rather than a degradation of other changes to the lower urinary tract that can impact on the magnitude and extent of voiding function.
List of abbreviations (see also legend to figure 1 for derived parameters and variables)

$P_{\text{det}}$ subtracted detrusor pressure

$P$ $P_{\text{det}}$ – (baseline $P_{\text{det}}$ prior to isovolumetric pressure rise).

$P_0$ calculated maximum isovolumetric pressure

$v_{\text{CE}}$ calculated maximum velocity of contractile element shortening

BCI bladder contractility index

DCP detrusor contractility parameter

$T$ bladder wall tension

$Q$ flow

BOOI bladder outflow obstruction index

$t_{20-80\%}$ duration of 20-80% isovolumetric contraction interval

$k$ bladder wall stiffness

Notes: upper case $P$ denotes pressure, rather than lower case $p$ as often used in urodynamics recordings. This is to avoid confusion with the p-value used to denote levels of statistical significance. Lower case $v$ is used to denote velocity to avoid confusion with $V$ as often used in urodynamics for volume.
References


5. Sarnoff SJ. Myocardial contractility as described by ventricular function curves; observations on Starling's law of the heart. Physiol Rev 1955; 35: 107-122.


Figure 1. Urodynamic recordings of subtracted detrusor pressure, \( P_{\text{det}} \), and flow, \( Q \), from which variables were measured. A: recordings over the time-frame of an entire bladder contraction defining values of \( \Delta P_{\text{det}} \), \( P_{\text{det max}} \), \( P_{\text{det time}} \) and \( \text{Flow time} \). The baseline \( P_{\text{det}} \) value is also shown. B: faster time scale of the rise of the \( P_{\text{det}} \)-transient defining values of \( \Delta P_{\text{ISV}} \), \( P_{\text{detQ init}} \), \( P_{\text{detQ max}} \) and \( Q_{\text{max}} \). Also shown are the pressure values for 20 and 80\% of \( \Delta P_{\text{ISV}} \), from which the 20-80\% \( P_{\text{ISV}} \) time was calculated.

Figure 2. Smoothing protocols of pressure rises. A: The rising phase of a voiding \( P_{\text{det}} \)-transient, either unsmoothed (\( P \)) or smoothed with greater running average intervals (See Methods, equation 1). The particular record was sampled at 50 Hz so that running averages over 10, 20, 50 or 100 points generated traces averaged over 0.2, 0.4, 1.0 or 2.0 s (\( P_n = P_{10-100} \)). B: Plots of running averaged traces (\( P_n \)) as a function of the unaveraged trace (\( P \)). The line of identity is also drawn.

Figure 3. Derived contractility measures vs urodynamic variables. Plots of \( \nu_{CE} \) as a function of age (part A); \( t_{20-80\%} \) (part B); \( Q_{\text{max}} \) (part C) and BCI (part D). The relation between \( P_0 \) and \( \Delta P_{\text{ISV}} \) is shown in part E. Data are shown separately for male participants (closed squares) and female participants (open squares).

Table I. Demographic and urodynamic data, and derived contractility indices, of subjects contributing to the study. Median data with 25, 75\% interquartiles, \( n=\)number of patients
Figure 1

A

$P_{\text{det}}$ \(20\ \text{cmH}_2\text{O}\)

$Q$, 2 ml s\(^{-1}\)

$P_{\text{det, max}}$

$\Delta P$

$P_{\text{time}}$

B

$P_{\text{det}}$ \(20\ \text{cmH}_2\text{O}\)

$Q$, 2 ml s\(^{-1}\)

$\Delta P_{\text{isv}}$

$P_{\text{det, init}}$

$P_{\text{80\%}}$

$P_{\text{20\%}}$

$Q_{\text{max}}$

$Q$

Baseline $P_{\text{det}}$

$10\ s$
Figure 2

A

B

Pn, cm H₂O

P, cm H₂O
Figure 3

A

$\nu_{CE} \text{ s}^{-1}$

Age, years

0 20 30 40 50 60 70 80

B

$\nu_{CE} \text{ s}^{-1}$

t$_{20-80}$, s

0 5 10 15 20

C

$\nu_{CE} \text{ s}^{-1}$

$Q_{max}$, ml.s$^{-1}$

0 5 10 15 20 25 30 35

D

$\nu_{CE} \text{ s}^{-1}$

BCI

0 50 100 150 200 250

E

$P_{o}$, cmH$_2$O

0 50 100 150 200

$\Delta P_{LV}$, cmH$_2$O

0 50 100 150 200
Table 1. Demographic and urodynamic data, and derived contractility indices, of subjects contributing to the study. Median data with 25, 75% interquartiles, n=number of patients.

<table>
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<tr>
<th>Clinical characteristics</th>
<th>All data (n=40)</th>
<th>Male (n=21)</th>
<th>Female (n=19)</th>
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<tr>
<td>Age, years</td>
<td>54.5 [45, 65]</td>
<td>62 [51, 66]</td>
<td>53 [39, 56]</td>
</tr>
<tr>
<td>Δp, cm H₂O</td>
<td>38.5 [20.8, 55.6]</td>
<td>39.3 [24.7, 60.3]</td>
<td>34.5 [18.0, 44.8]</td>
</tr>
<tr>
<td>p @ Qinit, cm H₂O</td>
<td>33.9 [19.7, 41.1]</td>
<td>34.0 [22.7, 56.7]</td>
<td>31.0 [17.1, 36.8]</td>
</tr>
<tr>
<td>Δp iso, cm H₂O</td>
<td>25.4 [13.8, 32.8]</td>
<td>27.5 [14.9, 44.5]</td>
<td>19.4 [13.7, 28.4]</td>
</tr>
<tr>
<td>Qmax, ml.s⁻¹</td>
<td>11.2 [7.9, 20.2]</td>
<td>10.8 [6.5, 19.4]</td>
<td>11.6 [8.4, 22.2]</td>
</tr>
<tr>
<td>p @ Qmax, cm H₂O</td>
<td>38.1 [22.7, 48.3]</td>
<td>41.9 [30.7, 54.4]</td>
<td>35.6 [19.2, 43.6]</td>
</tr>
<tr>
<td>BOOI</td>
<td>9.6 [-13.2, 32.3]</td>
<td>20.0 [-11.1, 40.1]</td>
<td>-0.8 [-15.5, 16.7] *</td>
</tr>
<tr>
<td>V @ Qinit, ml</td>
<td>250 [225, 282]</td>
<td>229 [203, 249]</td>
<td>282 [250, 313]</td>
</tr>
<tr>
<td>p duration, s</td>
<td>53.0 [25.9, 76.6]</td>
<td>52.0 [26.2, 90.0]</td>
<td>53.0 [29.1, 72.5]</td>
</tr>
<tr>
<td>Q duration, s</td>
<td>31.8 [21.7, 42.0]</td>
<td>28.0 [23.0, 37.0]</td>
<td>34.0 [19.5, 51.5]</td>
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<td>t₀-100% s</td>
<td>8.5 [5.2, 12.0]</td>
<td>8.7 [4.5, 12.3]</td>
<td>8.1 [5.4, 11.7]</td>
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<tr>
<td>t₁₀-90% s</td>
<td>4.0 [2.9, 6.7]</td>
<td>5.2 [3.3, 7.6]</td>
<td>3.5 [2.7, 5.4]</td>
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<tr>
<td>t₂₀-80% s</td>
<td>3.0 [1.9, 4.7]</td>
<td>3.6 [2.0, 6.0]</td>
<td>2.8 [1.9, 4.0]</td>
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<tr>
<td>dP/dtmax iso, cm H₂O.s⁻¹</td>
<td>6.8 [4.8, 9.8]</td>
<td>7.2 [4.7, 9.1]</td>
<td>6.8 [4.3, 10.3]</td>
</tr>
</tbody>
</table>

Contractility indices, voiding contractions

| V CM, s⁻¹ | 1.19 [0.78, 2.04] | 1.17 [0.78, 1.94] | 1.21 [0.87, 2.11] |
| p₀, cm H₂O | 30.2 [21.5, 44.3] | 39.1 [24.6, 63.5] | 27.9 [20.6, 36.4] |
| T₀, N     | 68.9 [44.1, 89.1] | 69.2 [52.2, 110.2] | 59.3 [38.7, 74.3] |
Rationale of phase-loop analysis to calculate $v_{CE}$ and $P_0$.

The use of $(dP/dt).P^{-1}$ at zero load as an index of contractility follows from the Hill model for muscle contraction. A contractile, or force-generating, element (CE) lies in series with a series elastic component (SEC); the whole lying in parallel to a parallel elastic component (PEC). During an isometric contraction the rate, $v$, of CE shortening is equal to the rate of SEC lengthening so that: $v_{CE} = v_{SEC} = |dl_{CE}/dt| = |dl_{SEC}/dt|$; where $l$ is the length of CE or SEC. The term $v_{SEC}$ represents the rate of change of wall stress, $s$, per unit amount of stress, and is normalised to a stiffness constant for the tissue, $k$. Thus, $v_{CE} = v_{SEC} = ds/dt = (k.s)^{-1}$. Laplace’s Law shows that intravesical pressure, $P$, is proportional to wall stress under isovolumetric conditions, with an arbitrary constant, $X$, so that: $v_{CE} = (X dP/dt) = (k.X.P)^{-1} = dP/dt = (k.P)^{-1}$. A plot of $(dP/dt).P^{-1}$ as a continuous function of $P$ throughout an isovolumetric contraction will yield a force (pressure)-velocity plot that will yield an extrapolated maximum value of $v_{CE}$ at zero load (where the plot intercepts the $(dP/dt).P^{-1}$ axis at $P=0$) and an extrapolated maximum value of $P (P_0)$, where the plot intercepts the $P$ axis as $v_{CE}$ is zero.

Several assumptions and calculations were included.

1. It is assumed that the bladder is ellipsoid or spherical during isometric contraction and the rate of intravesical pressure change by Laplace’s Law is proportional to the rate of contractile element shortening

2. Contractile component tension is equal to series elastic (SEC) tension soon after activation. However, appreciation of PEC stress-strain properties is also needed as the PEC carries part of the resting tension and is only transferred to the SEC/CC fraction when CC shortening has been carried out. This may be accounted for by subtracting the absolute value of resting
tension (pressure) from values during isometric contraction and this was done in the measurement presented here.¹

3. The series elastic tension is scaled by a stiffness parameter, k, that is assumed to be constant throughout. Whether k is equivalent or proportional to the reciprocal of bladder compliance during filling has not been determined and has been added to the 'limitations' section. However, this limitation will apply to any measurement of intravesical pressure during a contraction.

Supplementary Figure 1 shows a modelled bladder contraction (part A) and a plot of \( (dP/dt)^{-1} \) as a function of P (Part B). The plot can be fitted by a hyperbolic function equivalent to a Hill force-velocity relationship; \( (p+a)(v+b)=k(p_0+a) \). Here a and b are constants, \( P_0 \) is the maximum value when \( v_{CE} \) (equivalent to \( (dP/dt)^{-1} \)) is zero and the intercept on the \( (dP/dt)^{-1} \) axis is equivalent to maximum \( v_{CE} \).

Supplementary Figure 1. Derivation of the method to estimate muscle contractility. A model contraction (part A) and a derived \((dP/dt).P^{-1}\) vs \(P\) (part B). The line in part B is fitted to the equation of the hyperbola \((p + a)(v + b) = b(p_0 + a)\) and extrapolated to the \(P\)-axis and \((dP/dt).P^{-1}\) axis to yield respectively values of \(P_0\) and \(v_{CE}\).
Validation of the analysis using an inotropic agent with isolated perfused pig bladders.

Experiments used arterially perfused pig bladders to demonstrate the action of a known inotropic agent carbachol, added to the perfusate, on intravesical pressure and also on $v_{CE}$ and $P_0$. The bladder was held at constant volume to generate isovolumetric contractions, as measured in the human subjects. Pressure recordings were less prone to external interference than recordings with humans and so provided a convenient validation model.

Methods. Female pig bladders were obtained at a local abattoir. The distal abdominal aorta and branches supplying the bladder were carefully dissected free. The bladder and associated vasculature were then excised and perfused with ice-cold Ca-free Krebs’ solution at 4°C to drain blood from the organ and transported to the laboratory in cold (4°C) solution for immediate use. *Ex vivo* intravesical pressure recordings were made from arterially-perfused pig bladders at 37°C and filled to 150 ml. Isovolumetric contractions were elicited by injections of carbachol-Krebs’s into the perfusion-line. Digitised recordings were recorded at 10 kHz and retrieved at 0.4 kHz for analysis. The composition of Krebs’s solution was (mM):

$$\text{NaCl, 118.3; NaHCO}_3, 24.9; \text{KCl, 4.7; MgSO}_4, 1.15; \text{KH}_2\text{PO}_4, 1.15; \text{CaCl}_2 1.9; \text{D-glucose, 11.7, gassed with 95% } \text{O}_2/5\% \text{ CO}_2, \text{pH } 7.38 \pm 0.01, 36\pm1°C).$$

Results. Pressure transients were recorded, at a constant intravesical volume of 150 ml, in response to the contractile agonist, carbachol (30-1000 µM). Supplementary Figure 2A shows superimposed rising phases of pressure transients and their first derivatives in response to carbachol. Corresponding $(dP/dt).P^{-1} vs P$ plots are in part B and show that increased contractions and $dp/dt_{\text{max}}$ values with rising carbachol concentrations were mirrored by increases of $v_{CE}$ and $P_0$ (part B). Part C shows the concentration-dependence of $v_{CE}$, and $dp/dt_{\text{max}}$. In addition, $v_{CE}$ was inversely related to values of $t_{20-80}$, as in human data.
Supplementary Figure 2. Contractility variables in the *ex vivo* pig bladder. A: Isovolumetric pressure traces from perfused pig bladder during bolus injections of carbachol (30-1000 µM): also shown are the first derivative \( \frac{dp}{dt} \) of the traces. B: plots of \( \frac{dP}{dt} P^{-1} \) as a function of \( P \) for the traces in part A. C: carbachol dose-dependence of \( v_{CE} \) (open squares) and \( \frac{dP}{dt}_{max} \) (closed circles) and \( t_{20-80\%} \) (closed squares). Lines are those of best-fit.

Reference