Mechanical properties of the human uterine cervix: An in vivo study

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Abstract

Experimental results of in vivo measurements to characterize the mechanical behaviour of human uterine cervices are documented. Aspiration experiments were performed on eight uteri in vivo, before vaginal/abdominal hysterectomy, and four uteri were also tested ex vivo, approximately 1.5 h after extraction. The reproducibility of the mechanical data from the in vivo aspiration experiments has been analysed. For an introduced “stiffness parameter” the organ specific SD is 22%, so that the proposed experimental procedure allows detections of 30% changes with respect to a reference value of the stiffness parameter. A comparison of in vivo and ex vivo data from the same organ has shown that: (i) the ex vivo mechanical response of the uterine cervix tissue does not differ considerably from that observed in vivo; (ii) some differences can be identified in tissue pre-conditioning with ex vivo showing a stronger history dependence with respect to in vivo; (iii) the differences in the time dependence of the mechanical response are not significant and might be masked by the variability of the measured data. This study represents a first step of a clinical application aiming at analysing the mechanical response of normal cervical tissue at different gestational ages, and identifying the mechanical properties that characterize pathologic conditions such as cervical insufficiency leading to preterm delivery.

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1. Introduction

The identification of the mechanical properties of soft biological tissues is essential to the understanding of their functions, and, therefore, to a number of medical applications such as diagnosis, surgery planning and training of surgical procedures with virtual reality-based simulators (see, e.g., Avis, 2000; Greenleaf et al., 2003; Picinbono et al., 2002; Snedeker et al., 2002; Szekely et al., 2000; Szekely, 2003). In particular, experimental data obtained from appropriate in vivo measurements that mimic real loading conditions in a physiological environment might be essential to develop new diagnostic devices. In vitro studies are sometimes not appropriate to characterize the response of a soft biological tissue in its in vivo environment, since after removal from its natural biochemical milieu with blood supply and hormone stimuli the mechanical properties of the tissue may change in a significant way. Very limited quantitative data are available to describe the mechanics of soft biological tissues in vivo because of the severe technical and ethical problems related to the experiments.

Qualitative evaluation of the mechanical properties of soft biological tissues through palpation is an established practice in medicine. Specifically the palpation
of the uterine cervix represents a standard procedure, which is applied during regular pelvic examination. During labor the cervix is palpated in order to check its length, shape, consistency and tenderness (Bishop, 1964). In the case of abnormal findings, like cervical insufficiency, medical imaging techniques such as vaginal ultrasound examination are used (Tongsong et al., 1995). Another example of mechanical evaluation for diagnostic purposes is elastography (Manduca et al., 2001; Ophir et al., 1991). This method complements the information from ultrasound examination by providing qualitative data on differences in stiffness between tissues of internal organs. In this way lesions or diseases can be identified that do not possess echogenic properties.

Quantitative local measurements of mechanical properties of tissues have the potential to provide a method for (more) accurate tissue classification and early detection of diseases. To the authors knowledge, the first quantitative mechanical measurements on human organs in vivo were performed by Carter et al. (2001) with indentation experiments on human liver. A number of different procedures for quasi-static in vivo tissue testing of human and animal soft organs have been recently developed. They are based on indentation, aspiration or shear testing (see, e.g., Hendriks et al., 2003; Kalanovic et al., 2003; Kauer et al., 2002; Miller et al., 2000; Nasseri et al., 2002; Ottensmeyer, 2002; Tonuk and Silver-Thorn, 2004; Zheng and Mak, 1996).

The main limitation in the application of quantitative mechanical data for diagnostic purposes is caused by the scatter of the mechanical properties typically observed between patients as well as between different locations in one single organ: SDs in the range of 50% or more are reported in the literature (see, e.g., Carter et al., 2001; Nava et al., 2004a; Snedeker et al., to appear). Scatter of mechanical data is not only due to the natural variability of the mechanical behaviour coming from the non-homogeneity of the biological tissues, but also to the uncertainties and shortcomings of experimental procedures. In particular, in vivo testing during surgical intervention leads to non-ideal conditions that might increase the inherent uncertainty, as compared with bench top ex vivo experiments performed in the laboratory.

In the present study, an “aspiration device” (Vuskovic, 2001) has been used to characterize the in vivo mechanical properties of human uterine cervices. The experimental procedure, using the aspiration device, controls the kinematic and kinetic boundary conditions so that identical aspiration experiments can be repeated several times for the same tissue sample (Nava et al., 2004a). Recently, the device has been used for intra-operative measurements on human uteri, and the experimental data were used in the inverse finite element characterization of the related mechanical properties (Kauer et al., 2002).

The aspiration device allows the assessment of the mechanical response of internal organs under sterile conditions without harm to the tested tissue. The approach described in this paper might therefore complement clinical palpation and ultrasound examination of the cervix and serve for diagnosis. The present work is the first application of the aspiration device in a clinical study. The scatter of the mechanical data obtained from intra-operative experiments has been evaluated in order to verify the feasibility of in vivo measurements on human uterine cervices.

For this purpose eight human uteri were tested in vivo, before vaginal/abdominal hysterectomy, and four of them were also tested ex vivo, approximately 1.5 h after extraction. Preliminary experimental results are presented and conclusions are proposed on the sensitivity of the present procedure for the detection of changes in the mechanical behaviour of cervices. The experiments were performed at the Department of Obstetrics and Gynecology at Medical University Graz in Austria.

2. Experiments and data analysis

2.1. Aspiration device

The device for the quasi-static aspiration tests is an improved version of the apparatus originally developed by Vuskovic (2001) (for the improved device and aspiration experiments of human liver and kidney see the recent work by Nava et al., 2004a). The working principle of the device is illustrated in Fig. 1 and is based upon the pipette aspiration technique (Aoki et al., 1997). The device consists of a tube in which the internal pressure can be controlled according to a desired pressure law. The design was driven by issues such as safety, sterilizability, space limitation and a short data acquisition time, which are important when dealing with in vivo applications.

The experiment is performed by (i) gently pushing a tube against the tissue to ensure a tight initial contact and (ii) creating a (time variable) vacuum inside the tube so that the tissue is sucked through the aspiration area (with a diameter of 10 mm), see Fig. 1.

For an isotropic and homogeneous tissue, a complete description of the tissue deformation field can be obtained by monitoring the side-view profile of the tissue during the vacuum change. An optical fibre, which is connected to an external source of light, provides the necessary illumination in the inner part of the tube. The images of the side-view (for an example, see Fig. 2) are reflected by a mirror and are captured at a frequency of 25 Hz by a digital camera mounted on the upper part of the device. The grabbed images are analysed off-line in order to extract the profiles of the
deformed tissue (Fig. 3). The present image acquisition and analysis technique allows tissue vertical displacement to be measured with an accuracy of 0.05 mm. A standard personal computer (running NI LabView Version 6.1) controls the pressure inside the device by means of a pump, an air reservoir and two valves.

The duration of the loading and unloading cycles is about 20 s and the magnitude of the vacuum (maximum allowed to be 400 mbar absolute pressure or 600 mbar negative relative pressure) is selected in order to avoid tissue damage due to excessive deformation. Time histories of measured pressure and deformation profiles constitute the input data used to evaluate the mechanical properties and to determine the constitutive model. From the analyses of experimental data, constitutive models can then be determined through iterative finite element calculations. In Nava et al. (2004a,b) non-linear viscoelastic models have been used to describe the mechanical response of animal and human organs tested ex vivo with the aspiration device. The corresponding finite element calculations have shown that significant deformations are achieved in the tissue for superficial
and deeper layers, down to a depth of approximately 5 mm.

2.2. Uterine cervix

The uterus is a fibro-muscular organ dividable into an upper part of the uterine body (corpus) and a lower constricted segment (cervix). The most important biological functions of the cervix are the conservation of the developing pregnancy and the effacement and relaxation for delivery at the right time. Fig. 4 represents the anatomy of the uterus and shows the cervix projecting through the anterior wall of the vagina. The lower part of the cervix (vaginal portio) is usually 1 cm long and has a convex round surface with a centric opening (external orifice) bounded by two lips. During the measurements, the aspiration device was placed on the anterior lip, as indicated in Fig. 4.

The cervix is composed of columnar epithelium, which lines the endocervical canal, and squamous epithelium, which covers the outside of the portio. The point at which they meet is called the junction of the portio, which in the case of a menopausal woman (the uteri investigated) always lies in the cervical canal and is not present on the visible surface of the portio (Berek, 1996). Therefore, the aspiration device was exclusively placed on squamous epithelium.

2.3. Experimental procedure

All patients were asked to take part in the study and informed consent was given by all participants.

In vivo experiments were performed after anesthesia and some pre-surgical procedures (evacuation of the urine, cleaning and disinfection of the cervix and the surrounding vagina). Specula were inserted to get access to the cervix. Under visualization of the cervix, the device was placed at the upper lip (see Fig. 4), and was then kept in contact with the tissue (on the same spot) to achieve optimal results.

Four of the eight uteri (number 2, 3, 5, and 7, see Table 1) were tested ex vivo, approximately 1.5 h after the extraction. The uteri were kept in a closed plastic container inside the operation room at ambient temperature. No solutions were used for tissue conservation. Ex vivo tests were performed at the same testing location as for the in vivo experiments. The aspiration device was in contact with the table and the uterus was gently pressed against the aspiration area, see Fig. 5. The remaining four uteri were not available for ex vivo

<table>
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<tr>
<th>Uterus number</th>
<th>Age</th>
<th>Given births</th>
<th>Abortions</th>
<th>Pathology</th>
<th>Hormonal replacement therapy</th>
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<td>3</td>
<td>0</td>
<td>Endometrial cancer</td>
<td>Yes</td>
</tr>
</tbody>
</table>
testing because they had to be dissected during the vaginal hysterectomy procedure to complete surgery.

2.4. Experimental protocol

Testing conditions in the aspiration experiment are characterized by:

(i) the pressure history of the loading–unloading cycles, and, in particular, the minimum relative pressure of the cycle;
(ii) the number of loading–unloading cycles;
(iii) the resting time between loading–unloading cycles.

Eight uteri were tested in vivo, before hysterectomy. In general, the following protocol was adopted for in vivo testing:

(a) First test: one single loading–unloading cycle was performed, Fig. 6(a). The pressure began at atmospheric pressure, reached a minimum of $p_{\text{min}} = 220$ mbar negative relative pressure, was maintained at that pressure level (with oscillations about 220 mbar) for approximately 8 s and was then returned to atmospheric pressure.

(b) Second test: one single loading–unloading cycle, the same cycle as in the first test. This experiment was performed in order to assess the repeatability of the results by a direct comparison with the first test.

(c) Third test: four to five loading–unloading cycles, in which the cycle of Fig. 6(a) was applied consecutively (Fig. 6(b)). The resting time between individual cycles was approximately 10 s.

Four uteri were tested ex vivo, approximately 1.5 h after extraction. The same tests (a)–(c), as described above, were also performed ex vivo, with the addition of the following test:

(d) Fourth test: three loading–unloading cycles, each cycle with the pressure history given in Fig. 6(a). The resting time between the cycles was 30 s.

The number of loading and unloading cycles and the resting time of 10 s between the cycles were selected in order not to exceed a total duration of each test of approximately 2 min. During the test, the operator holds the aspiration device against the tissue with a constant compression force. Preliminary tests with in vivo measurements showed that after 2 or 3 min the compression force applied by the operator tends to diminish significantly. Experiments with longer duration (approximately 3 min for the test (d) described above) were performed ex vivo, since the operator could lean on the table.

For the same organ the tests were always repeated at the same location, i.e., the aspiration device was placed on the upper lip of the cervix at the 12 o’clock position, see Fig. 4. A slight imprint remained on the tissue after performing the aspiration experiment so that the testing location could be identified. In this way, the same location could then be selected for ex vivo measurements.

2.5. Clinical data

All tested cervices were of menopausal women. For each patient, the following data were recorded: age, number of births, abortions, pathology and hormonal replacement therapy. Data are reported in Table 1.

2.6. Data analysis

The deformation profiles obtained from the aspiration experiments were processed to extract the displacement history of the highest point of the profile, i.e., the
point P indicated in Fig. 2. Fig. 7 shows representative plots of the displacement history of point P for one cycle and for multiple cycles. Specific features of the deformation history are identified such as the locations A, B, C, D, and the displacement history between B and C, used for data analyses and comparison purposes. In particular, the following points are defined:

Point A: displacement immediately before the pressure decreases.
Point B: displacement at which minimum pressure is reached.
Point C: maximum displacement in the first load cycle (before pressure increases again).
Point D: maximum displacement at the 4th load cycle.

The initial displacement is typically within the range of 1–2 mm, and is due to the compressive force exerted when pushing the tube against the tissue. Typically, the maximum relative displacement in each cycle (difference between the displacement at A and C, Fig. 7) is within the range of 1–3 mm.

The displacement histories can then be characterized by a relatively low number of characteristic parameters. With reference to the displacement levels A–D (indicated in Fig. 7), the following parameters are defined:

- $d_0$: displacement at B – displacement at A
- $d_1$: displacement at C – displacement at A
- $d_4$: displacement at D – displacement at A

We propose that the curve between the levels B and C is interpolated by an exponential function, with the origin shifted to location B, i.e.,

$$f(t) = A_0 \left(1 - \exp\left(-\frac{t}{\tau}\right)\right)$$

with $A_0 = (d_1 - d_0)/(1 - \exp(-t_0/\tau))$, where $\tau$ is the characteristic time (in seconds) of the exponential function (referred to as “rising time”), which was determined from the first cycle of the experimental curves, and $t_0$ is the time between the points B and C ($t_0 = 8$ s). The four parameters $d_0$, $d_1$, $d_4$ and $\tau$ are determined from measured values and characterize the displacement history. Together with the known values of the applied negative pressure history, these parameters enable evaluation and comparison of the different mechanical responses of the organs. For subsequent data analysis, it is useful to introduce three additional parameters, i.e., the so-called “stiffness” $\eta$ in bar/mm, and two dimensionless quantities, the so-called “softening” $\gamma$, and “creep” $\delta$, defined to be

$$\eta = \frac{p_{\text{min}}}{d_1}, \quad \gamma = \frac{(d_4 - d_1)}{d_1}, \quad \delta = \frac{d_4}{d_0}.$$ 

For data analysis of the ex vivo test (d) (see Section 2.4) the dimensionless softening parameter

$$\gamma_3 = \frac{(d_3 - d_1)}{d_1}$$

is introduced, where $d_3$ is the maximum displacement of the third cycle.

The measured parameters $\eta$, $\delta$, and $\tau$ are analysed from a statistical point of view, calculating mean values and SDs and assuming a Gaussian distribution of the data. In particular, in order to eliminate the organ to organ variability, the measured values of each organ were normalized with respect to the organ specific average in vivo value.

3. Results

3.1. Stiffness $\eta$

Fig. 8 shows the stiffness values $\eta$ in bar/mm calculated from the data obtained from eight uterine cervices.
Several values of $\eta$ were determined for each cervix by evaluating the data from tests (a), (b) and the first cycle of tests (c) and (d), as described in Section 2.4. Diamond symbols indicate values obtained from in vivo tests, while squares refer to the results obtained from four cervices tested ex vivo. From these data, the average stiffness $\eta_{\text{ave}}$ and the related SD $\sigma_{\eta}$ were calculated for each organ considering in vivo as well as ex vivo results. Fig. 8 illustrates the average stiffness values and the related error-bars indicating the range of SD, for each organ.

Next, the average of the stiffness parameter over all organs (from in vivo and ex vivo data) and the corresponding SD were calculated. The corresponding distribution of $\eta$ is represented in Fig. 9 (dashed line). The solid lines in Fig. 9 correspond to the distribution obtained from all ex vivo data (black) and from all in vivo data (grey).

Normalized distributions of the stiffness parameter were obtained by dividing each $\eta$ value by the organ specific average in vivo stiffness. The results for in vivo and ex vivo data in terms of mean value and SD (indicated as error bars) are reported in Fig. 10. Note that the mean value for the normalized in vivo data is 1 by definition.

Assuming a variance component model and treating in vivo and ex vivo data as equally valid, the variability of measured data can be defined as (i) the SD $\sigma_{\lambda}$ for the eight uteri (which depends on the uterus to uterus variability), and (ii) the SD $\sigma_{B}$ for each organ (a measure of the errors in the measurement procedure). For the

Fig. 8. Stiffness parameter $\eta$ calculated from the measurements on eight uterine cervices. Diamond symbols indicate values obtained from in vivo tests; squares refer to the results of ex vivo tests performed on four uteri. Average values and SDs are reported for each organ considering in vivo as well as ex vivo results (error bars indicate the mean value ± SD).

Fig. 9. Gaussian distributions of the stiffness parameter $\eta$ for all measurements (in vivo and ex vivo), for in vivo data and for ex vivo data.

Fig. 10. Mean values and SDs (error bars indicate ± SD) of the parameters $\eta$ (stiffness), $\delta$ (creep), and $\tau$ (rising time) normalized with respect to the corresponding organ specific average in vivo value. Results from in vivo and ex vivo data are represented by a column with line pattern and pointed pattern, respectively.
stiffness parameter $\eta$ these SDs were calculated to be: $\sigma_A = 32\%$, $\sigma_B = 22\%$. Based on these results predictions can be made on the capability of this experimental procedure to detect a certain change in the parameter $\eta$. In a clinical study, the initial average stiffness value of a specific organ (reference stiffness) can be determined by repeating the measurement several times, for example, five times. Fig. 11 shows the detection rate as a function of the changes in the stiffness parameter $\eta$ of one patient by assuming five measurement repetitions for each inspection.

### 3.2. Softening $c$

The softening parameter $c$ relates the mechanical response in the fourth cycle with the response obtained during the first cycle. A comparison of $c$ obtained from in vivo data with respect to the corresponding values from ex vivo data is reported in Fig. 12. For each of the organs tested ex vivo (uteri 2, 3, 5 and 7) the $c$ value from in vivo measurements is reported on the horizontal axis, whereas the corresponding ex vivo value is on the vertical axis. The solid line represents the locus of equal in vivo and ex vivo values. Hence, if there were not difference between the in vivo and ex vivo values, all four data points would lie on this line.

### 3.3. Creep $d$ and rising time $\tau$

The time dependence of the mechanical response is evaluated from the displacement history of the time period with “constant” pressure during the first loading cycle. It should be emphasized that, although the external load is kept approximately constant, stresses in the tissue will change, and, therefore, the parameters $d$ and $\tau$ cannot be directly associated with the creep compliance of the material.

As for the stiffness values, normalized distributions were calculated for $d$ and $\tau$ and the corresponding data in terms of mean values and SDs for in vivo and ex vivo measurements are reported in Fig. 10.

### 3.4. Short versus long resting times

Under ex vivo conditions, experiments were performed also with three loading–unloading cycles with...
resting time between the cycles of 30 s, i.e., test (d), see Section 2.4. It is of interest to compare the “softening” behaviour under these conditions with that observed in the corresponding multiple cycle tests with a resting time of 10 s. To this end, the parameter $c$ has been calculated from the maximum displacement of the third cycle of the tests (c) and (d).

A comparative study is reported in Fig. 13. For each of the organ tested ex vivo (uteri 2, 3, 5 and 7) the $c$ value from test (c) (long resting time) is reported on the horizontal axis, whereas the corresponding value from test (d) (short resting time) is on the vertical axis. Similar to Fig. 12, the solid line represents the locus of equal softening values for long and short resting times.

4. Discussion

4.1. Stiffness

The values of the stiffness parameter $\eta$ vary from a minimum of 0.065 (uterus 6) to a maximum of 0.315 bar/mm (uterus 3), see Fig. 8, which gives a factor of 4.8 between these values. The average values of each uterus range from 0.095 (uterus 2) to 0.24 bar/mm (uterus 3) which gives a factor of 2.5. The maximum SD $\sigma_\eta$ for each organ is 30% (uterus number 6). These results indicate that the scatter of the $\eta$ values between the different organs is larger than the scatter of the measurement results obtained from one single organ.

Fig. 9 shows the Gaussian distribution of the $\eta$ values over all measured organs. The SD over all measurements is about 40% of the average stiffness value. Such scatter is common for mechanical measurements on soft biological tissue (see, e.g., Carter et al., 2001; Nava et al., 2004a; Snedeker et al., 2005). No appreciable difference in the average stiffness or SD from the distribution of all the in vivo and ex vivo data (considered separately) can be seen in Fig. 9.

In order to eliminate the organ to organ variability, the stiffness parameters of each organ were normalized with respect to the organ specific average in vivo stiffness (Fig. 10). The average of the normalized in vivo values is 1 (by definition) and its SD is 19%, whereas the average of the normalized ex vivo values is 1.045, with a SD of 27%. These results indicate that there is no significant difference between in vivo and ex vivo with respect to the stiffness parameter $\eta$. Thus, the overall mechanical response of the uterine cervix tissue measured ex vivo, approximately 1.5 h after extraction, seems to be representative of the in vivo behaviour. On the other hand history and time dependence of the material response changed to some extent from in vivo to ex vivo, as discussed later in this section. Gefen and Margulies (2004) have recently drawn similar conclusions from a comparison of in vivo and ex vivo indentation experiments on porcine brain: the short term mechanical response did not differ significantly but to some extent the long term relaxation behaviour did.

Since the measurements on each organ were all performed at the same location, the scatter of the normalized values of Fig. 10 may partly be due to the experimental set-up (experimental error). The scatter of in vivo data (SD: 19%) is smaller than that of ex vivo data (SD: 27%). This might be due to the fact that the aspiration device was kept in the same position for all tests performed in vivo on one organ, whereas the device was detached and re-contacted (at the same location) for each ex vivo experiment. One other possible reason for the larger variability of ex vivo data might be the lack of tissue perfusion (the tissue will not recover between tests as rapidly as in vivo). It may be concluded that for the stiffness parameter the experimental conditions for in vivo measurements did not increase the scatter of the aspiration tests results, this is a prerequisite for a possible application of this procedure for diagnostic purposes in an in vivo clinical study.

4.2. History and time dependence of the material response

The softening parameter $\gamma$ relates the mechanical response in multicycle aspiration experiments to the response obtained during the first cycle. Previous work has shown that the increase of the displacement with cycles is due to the history dependence of the mechanical tissue behaviour (Nava et al., 2004b). History dependence is associated with the phenomenon of “pre-conditioning” (see, e.g., Humphrey, 2002) and is mainly
known from observations in ex vivo tests. As shown in Fig. 7(b) after four to five loading–unloading cycles, the tissue still has not reached the “pre-conditioned” state (the maximum deformation is still increasing). Experiments with a larger number of cycles would allow characterization of the entire pre-conditioning phase. However, the duration of the experiment would be in the range of several minutes and, as discussed in Section 2.4, it would be difficult for the operator to fix the aspiration device with a constant compression force on the tissue for such a long time period.

The values of $\gamma$ obtained from in vivo experiments, as reported in Fig. 12, range from 0.05 to 0.19, whereas the corresponding values from ex vivo tests are between 0.11 (uterus 3) and 0.29 (uterus 2). The variability of $\gamma$ is comparable with that of the stiffness parameter $\eta$.

The results of Fig. 12 highlight a significant difference between in vivo and ex vivo mechanical response: all the points are consistently located at the upper left part of the diagram with ex vivo values of $\gamma$ larger than in vivo by a factor of approximately two. This is in agreement with the observations of Gefen and Margulies (2004): pre-conditioning was found to affect the mechanical response of porcine brain tissue to a larger extent ex vivo with respect to in vivo. Similar observations were also reported by Brown et al. (2003) from in vivo and ex vivo measurements on porcine abdominal organs.

Fig. 10 compares the distributions of the normalized values of $\delta$ and $\tau$ from in vivo and ex vivo experiments. The average value of the normalized creep parameter is smaller for ex vivo tests, whereas the corresponding normalized rising time is larger. However, the differences between in vivo and ex vivo are small and cannot be regarded as significant for the given scatter of the measured values.

The difference between the softening parameter $\gamma_3$ for long and short resting times in ex vivo experiments is shown in Fig. 13. All the points are located at the upper left part of the diagram since the softening parameter is always larger for short resting times. This might be attributed to the recovery characteristics of the tissue: with longer resting times microstructural processes lead to partial preservation of the initial material characteristics. Note that these observations were made on ex vivo experiments.

4.3. Constitutive modelling

No constitutive model has been derived from the experimental data yet. In the present work, the tissue behaviour has been analysed in terms of parameters that characterize the overall mechanical response, as measured with the proposed aspiration device. The parameter “stiffness”, “softening”, “creep”, “rising time” are phenomenological quantities used to compare the deformation curves obtained from the different experiments. They cannot be considered as material parameters: i.e., $\delta$ and $\tau$ cannot be directly associated with the creep compliance of the material; no elastic constant can be calculated from $\eta$; the softening parameter $\gamma$ refers to an increased deformation for the same applied negative pressure but it does not necessarily reflect a history-dependent reduction of the elastic moduli. This approach enables direct characterization of a biological tissue without going through computationally expensive numerical procedure for the solution of the inverse problem. The parameters proposed in this work can be evaluated quickly (almost “on-line”) with possible advantages for applications for diagnosis.

The design of a three-dimensional continuum model and the identification of the related parameters from the aspiration experiments represent challenging future steps of the present work. For this purpose, finite element procedures and optimization algorithms will be used that were successfully applied in previous work for the determination of parameters of a quasi-linear viscoelastic model from aspiration test results (see, e.g., Kauer et al., 2002; Nava et al., 2004a,b). A three-dimensional constitutive model of the cervix could be applied for the investigation of the organ mechanical behaviour under physiological loading conditions or for surgical simulation purposes. In addition, a constitutive model based on the histological tissue structure will provide further insights in the processes that govern tissue biomechanics. For example, discussions of the biomechanics of soft tissue in cardiovascular systems can be found in Holzapfel and Ogden (2003) or Humphrey (2002).

4.4. Limitations

The results of the stiffness parameter evaluation show that there is a scatter of measured data (SD up to 27%), which must partly be attributed to experimental uncertainties. The main source of uncertainty in the aspiration experiment is the force required to bring the device in contact with the tissue. The contact force determines the initial deformation of the tissue and any variation of this force during the measurement influences the time history of deformation. Modifications of the aspiration devices are under consideration to reduce and/or quantify the influence of the contact force on the measured results.

One other source of error is the oscillation of the pressure level around the prescribed minimum value, which is about ±10%. The mechanical analysis of the aspiration experiment with a suitable constitutive model (as discussed in Section 4.3) would allow quantification of the influence of this oscillation on tissue deformation. Improvements of the pressure control system are being implemented to significantly reduce the oscillation.
4.5. Applicability for diagnostic purposes

Although clinical palpation is a well established examination to reveal cervical changes, the method is not undisputable especially at late gestational ages, when introduction of bacteria into the cervical canal might cause severe problems. Additionally, palpation is based on individual experiences and detection of very early changes of cervical tissue, which is crucial in order to avoid preterm delivery, might not be achieved.

The use of the aspiration test performed during a routine speculum examination may provide “objective” information on the biomechanical properties of the cervix related to pathologic conditions. The analysis of the present data allows conclusions to be drawn on the expected sensitivity of the present technique. The sensitivity is assessed here from a statistical point of view using the data of the stiffness parameter \( \eta \), for which a much larger number of values could be determined from the present experiments as compared with the other parameters.

The analysis of the stiffness data with a variance component model assumes that measurements are repeated five times at each inspection and allows for a false positive detection rate of 15% (Fig. 11). The statistical distribution of the present data yields a positive predictive value of 90% for detecting a change by 1/3 of the initial stiffness value, or of 99% for detecting a change by 1/2 of the initial stiffness value.

Significant changes in the stiffness of the cervix are expected due to hormonal influences under, for example, hormonal replacement therapy and during pregnancy (Fung, 1993, p. 263ff, Rechberger et al., 1988), which might cause variations by one order of magnitude for the stiffness parameter \( \eta \). The present results support the application of the aspiration test to cervices of pregnant women in order to establish the mechanical properties of normal cervical tissue at different gestational ages. Future clinical studies on pre-menopausal subjects will determine the usefulness of the present technique for diagnosis.

5. Conclusions

The main purpose of the present study was to test the reproducibility of mechanical data obtained from aspiration experiments on human cervices with respect to a possible clinical application for diagnostic purposes. Future studies will be performed aiming at an application of the proposed method for the detection of early cervical changes associated with pathologic conditions.

Intra-operative in vivo measurements were performed on eight organs without delaying the surgical procedure. The quality of the in vivo data is comparable with that obtained ex vivo, and with the experience of previous ex vivo bench top applications of the aspiration device.

For four uteri, experiments were performed also ex vivo, after organ extraction. A comparison of in vivo and ex vivo data from the same organ has shown that: (i) the ex vivo mechanical response of the uterine cervix tissue, measured approximately 1.5 h after extraction, does not differ considerably from that observed in vivo; (ii) some differences can be identified in tissue pre-conditioning with ex vivo showing a stronger history dependence with respect to in vivo; (iii) the differences in the time dependence of the mechanical response (parameters \( \alpha \) and \( \tau \)) are not significant and might be masked by the variability of the measured data.

Our preliminary data indicate that the proposed stiffness parameter \( \eta \) can be used for the characterization of human uterine cervices since the experimental procedure enables to detect changes of 30% with respect to a reference stiffness value.

References


