In vivo measurement of tissue metabolism in tendons of the rotator cuff

IMPLICATIONS FOR SURGICAL MANAGEMENT


From the Nuffield Orthopaedic Centre, Oxford, England

We have undertaken an in vivo assessment of the tissue metabolism and cellular activity in torn tendons of the rotator cuff. Cellular oxygen consumption was measured in 13 patients undergoing mini-open repair of small, medium, large and massive full-thickness tears. Measurements were also taken from three control patients who were undergoing open stabilisation of the shoulder with grossly normal tendons. The level of oxygen and nitrous oxide was measured amperometrically using silver needle microelectrodes at the apex of the tear and 1.5 cm from its edge. With nitrous oxide indicating the degree of perfusion, oxygen consumption was calculated at each location to reflect cellular activity.

All of the torn tendons had lower levels of cellular activity than the control group. This activity was lower still in the tissue nearest to the edge of the tear with the larger tears showing the lowest activity. This indicated reduced levels of tissue metabolism and infers a reduction in tendon viability.

Our findings suggest that surgical repair of torn tendons of the rotator-cuff should include the more proximal, viable tissue, and may help to explain the high rate of re-rupture seen in larger tears.

The pathogenesis of tears of the rotator cuff remains unclear, but the condition is considered to be due to a combination of extrinsic impingement from structures surrounding the cuff and intrinsic degeneration from changes within the tendon itself. Recent pathological and genetic studies have emphasised the importance of intrinsic factors, but very little information is available regarding the process of degeneration of the rotator-cuff tendon.

Despite studies which have shown a critical, avascular zone within the rotator cuff 1 cm proximal to its insertion, it is not known whether the presumed hyperperfusion in this zone contributes to the development of the degeneration and ultimate failure of the tendon. Goodmurphy et al found that the vascularity of the edge of the tear was less than that in tissue 2.5 mm to 5.0 mm away from the edge. This contradicted the work of Fukuda, Hamada and Yamanaka who noted, in partial-thickness tears, that the critical zone of the tendon showed relative hyper-perfusion when compared with the proximal stump. Laser Doppler flowmetry studies have shown blood flow throughout the tendons of the rotator cuff and a hyperaemic response at the edge of the tear. Further evidence was provided by the observation that tissue adjacent to the edge of the tear (< 2.5 mm from the edge) appeared to be viable histologically in terms of its microvascular structure.

There are no studies which have measured cellular activity within the rotator cuff either in normal or pathological states. The only insight into cellular function within the tendon has been from conflicting studies into its synthetic capability.

Needle microelectrodes can be used to determine cellular activity by measuring oxygen consumption and tissue perfusion. For many years they have been used to monitor intravascular PO2 in neonates. More recently, they have been used to measure tissue perfusion in experimental studies on oxygen consumption in muscle tissue and to demonstrate differences in cellular viability within various tissues.

Single microneedle electrodes have subsequently been developed and used in vivo to determine the levels of oxygen and nitrous oxide simultaneously at the same site. These are polarised with specific voltages with respect to the anode used, and at these voltages oxygen and nitrous oxide are reduced and can be measured using current-voltage curves. Cellular activity can be calculated from these.
Our aim was to determine how cellular activity varied in the supraspinatus tendon according to the size of the tear and the distance from its edge.

Patients and Methods
The study group comprised 13 patients, seven men and six women who had a mini-open repair of a torn rotator cuff between 2003 and 2004. Their mean age was 55.6 years (41 to 63). There were three small, four medium, three large and three massive full-thickness tears (Table I), which were grouped at the time of repair according to the classification of Post, Silver and Singh.24 Three patients undergoing open stabilisation of the shoulder served as a control group, two men and one woman with a mean age of 33.3 years (27 to 38). Ethical approval was obtained for this study and all patients gave informed consent.

Method of measurement. Cellular activity was calculated by determining the concentration of oxygen and nitrous oxide within rotator cuff. The gases were delivered by general anaesthesia at known concentrations and their resultant tissue concentrations were measured amperometrically using a silver electrode, in which a 50 µm silver wire was epoxy-embedded into the lumen of an 18-gauge spinal needle, which served as the working electrode. A standard silver/silver chloride electrode served as the reference electrode. These were sterilised pre-operatively using gamma irradiation.

Oxygen was measured at a potential difference of -0.65 V across the working reference electrode circuit, while nitrous oxide was measured at -1.3 V. The polarising voltage was switched between -0.65 V and -1.3 V in cycles of 20 seconds. In this way the same electrode was able to record oxygen and nitrous oxide simultaneously at the same site, and at the same elapsed period from the time of ‘wash-in’ of inhaled general anaesthetic. This is an adaptation of the hydrogen wash-in principle25 and has been validated for use with both oxygen and nitrous oxide.26 Polarisation of the electrodes was achieved by a potentiostat (EMS Ltd, Oxford, United Kingdom) which controlled the cycling of the potential difference across the working and reference electrodes. The apparatus incorporated a medical grade head-stage to ensure that there was electrical isolation of the patient from the power supply. The measurements (mA) were recorded as current-time plots using an analogue-to-digital convertor (PowerLab; ADInstruments, Chalgrove, United Kingdom). The measured current was directly proportional to the partial pressure/concentration of each gas present in the tissue. Therefore for each measurement the concentration of the gas was determined from the previously produced calibration plot of current versus concentration for each electrode.

Measurement of oxygen. Two separate measurements were taken from each patient along a line 1 cm posterior to the leading edge of the supraspinatus tendon (Fig. 1). In the study group the first measurement was taken by placing the working electrode 0.5 cm from the edge of the tear and the second 1 cm more proximally, each at a depth of 0.5 cm. In the control group the first measurement was taken 1.5 cm from the insertion of the supraspinatus and the second 1 cm more proximally. During each of these separate measurements, the reference electrode was placed in the bulk of the deltoid. Each electrode was then calibrated in phosphate-buffered saline solutions which were equilibrated at pO2 and pN2O levels of 0%, 40% and 80% in order to establish the electrode’s calibration curves, as outlined above.

Cellular activity. This was defined as the difference between the diffusion coefficients of nitrous oxide (DN2O) and oxygen (DO2) determined from the measured gas concentrations for that tendon, divided by the diffusion coefficient of nitrous oxide in the measured tendon, i.e. (DN2O - DO2)/DN2O. For

<table>
<thead>
<tr>
<th>Case</th>
<th>Patient age</th>
<th>Duration of pre-operative symptoms (mths)</th>
<th>Tear</th>
<th>Distal tissue (Point 1)</th>
<th>Proximal tissue (Point 2)</th>
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<tr>
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Controls

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<th>Case</th>
<th>Patient age</th>
<th>Duration of pre-operative symptoms (mths)</th>
<th>Tear</th>
<th>Distal tissue (Point 1)</th>
<th>Proximal tissue (Point 2)</th>
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<td>93.63</td>
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<tr>
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simplicity, the difference in nitrous oxide and oxygen diffusivity was equivalent to the consumption rate of oxygen in the tendon, if the consumption rate of oxygen was modelled as a diffusive sink.

In order to determine the diffusion coefficients and the cellular activity in this way, it was necessary to construct a diffusion model for gases in the tendon using Fick’s law. Fick’s principle states that the rate of diffusion is proportional to the difference in concentration. The model was based upon an assumption of the existence of an essentially avascular region of supraspinatus tendon of 2 cm in length, situated proximally from the edge of the tear. Further, the model assumed that the blood supply along the length of the supraspinatus tendon provided more nutrients and gases, than at the edges of the tendon. Since all measurements were made at a depth of 0.5 cm, nominally half way through the tendon along the width centre-line, then the gas supply from the edges of the tendon could be ignored, enabling one-dimensional modelling to be made along the tendon length. For simplicity, it was also assumed that the section of avascular tendon was exposed to the same concentration of gases from each edge and that the entire tendon contained an equal concentration of oxygen and zero nitrous oxide before the point at which anaesthesia had been administered.

This simple diffusion model used the gas-concentration-time data from the in vivo microelectrode measurements and calculated the effective diffusion coefficients for nitrous oxide and oxygen which enabled calculation of cellular activity.

**Statistical analysis.** The cellular activity calculated from the proximal and distal points of measurement for small or medium and large or massive tears and the control group was compared using the Mann-Whitney U test. Comparisons made between the two measurement points from all groups were performed using the Wilcoxon signed-rank test. Differences in the age of the patients and the duration of pre-operative symptoms were compared using an independent t-test. A p-value ≤ 0.05 was considered to be significant.

**Results**

No adverse events or complications occurred in any of the patients in whom the rotator-cuff tendons were analysed using the microneedle electrodes. No statistical difference was found between the mean age of the patients and the pre-operative duration of symptoms for each size of tear. The cellular activity for each patient at both points was expressed as a relative percentage (Table I). There was an overall trend of decreasing cellular activity as the size of the tear increased, but this was not significant. The cellular activity within the tissue in the three control patients was seen to be universally high and similar values were seen for both measurement points in each patient (p = 0.2). Measurements from the patients with rotator-cuff tears showed that the tears of a smaller size had the highest cellular activity, and the lowest value was obtained from a massive tear. In two patients with a medium and two with massive tears, respectively, the cellular activity was similar for both measurement points. It was also noted that not all the smaller tears had universally high cellular activity and in three of the small and medium tears the cellular activity of the distal tissue was similar or worse than that in the larger tears. Additionally, the proximal tissue in the large tears was not dissimilar to that in the smaller tears. Both large and massive tears had reduced cellular activity at both measurement sites when compared with the corresponding sites in the control tissue (normal tendon). However, proximal tissue in medium tears had a similar level of cellular activity when compared with the control tissue although the tissue near to the edge of these tears showed lower cellular activity than the corresponding tissue in the control tendon.

Measurements taken at the edge of two of the massive tears had a negative value for cellular activity. This indicated that there was no oxygen consumption at this point, and that oxygen was accumulating which gave the negative value. Measurements in the proximal tissue in this group (point 2) were, however, calculated as positive values, although there was less activity than that in the tissue near the edge of the tear.

Figure 2 and Table II compare the median cellular activity in the proximal and distal tissue in the small to medium and large to massive tears and the control group. Proximal tissue in small and medium tears had high levels of cellular activity (84.07%), which was not significantly different.
from that seen in the proximal control tissue (p = 0.66). However, the cellular activity in the proximal tissue of large and massive tears (44.41%) was significantly lower than that seen in both the control tissue (p = 0.02) and the corresponding tissue of small and medium tears (p = 0.05). Measurements taken within the distal tissue showed a significant reduction in cellular activity in the small and medium tears (65.60%, p = 0.01) as well as the large and massive tears (44.40%, p = 0.02), when compared with the corresponding control tissue.

Overall, there was a significant reduction in cellular activity in the distal tissue of each patient in the study group when compared with the proximal tissue from the same tendon (p = 0.004).

**Discussion**

These results showed that the cellular activity decreased in full-thickness tears of the rotator cuff as the size of the tear increased, and that the tissue closest to the edge of the tear had a lower cellular activity than that which was more proximal. These changes were most dramatic in massive tears which showed a decrease in cellular activity in the distal tissue and in some specimens a level of activity compatible with inert tissue. The results indicated an overall deterioration in tissue quality in the rotator-cuff at the edge of the tear and poorer quality tissue as the size of the tear increased. This may help to explain the poor prognosis for patients with the largest tears.\textsuperscript{27-31} The findings also support the theory proposed by Codman,\textsuperscript{5} that intrinsic tendon degeneration was a major factor in tears of the rotator cuff. Harvie et al\textsuperscript{2} postulated that the mechanism for the genetic component was likely to be expressed at a cellular level. Yuan et al\textsuperscript{13} showed high levels of apoptosis in degenerate tears which have previously been shown to be under cellular and genetic control. Matthews et al\textsuperscript{1} and Hashimoto et al\textsuperscript{4} demonstrated a degenerative process histologically in full-thickness tears and that the degree of degeneration increased as the size of the tear increased. Our findings indicated that the torn tendon tissue had a reduced physiological capability which increased with the size of the tear.

In the tear groups there was a significant decrease in cellular activity in the more distal tissue which was most notable in massive tears. Two of three massive tears had negative values for cellular activity which indicated that oxygen was accumulating in this tissue when the measurements were taken. The tissue had lost its ability to metabolise oxygen effectively and the tendon tissue had become inert, with cells which were essentially dead. In some of the larger tears the ‘good’ proximal tissue was seen to have a lower cellular activity than that of the distal tissue in some smaller tears. These observations were not found in the normal tendon in which levels of cellular activity remained high throughout its length. The practice of excising a portion of distal tissue before repair is controversial, although widely practised, with histological and physiological evid-

![Bar chart showing the median cellular activity calculated from measurements taken at both points for the control group and the small or medium and large or massive tears.](image)

**Table II.** Comparison of cellular activity between tears of different size and the control group

<table>
<thead>
<tr>
<th>Tissue comparison</th>
<th>Relative (%)</th>
<th>p-value (when compared)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal control vs proximal small/medium</td>
<td>86.50 vs 84.07</td>
<td>0.66</td>
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<tr>
<td>Proximal control vs proximal large/massive</td>
<td>86.50 vs 44.41</td>
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<td>Proximal small/medium vs proximal large/massive</td>
<td>84.07 vs 44.41</td>
<td>0.05</td>
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<td>Distal control vs distal small/medium</td>
<td>94.83 vs 65.60</td>
<td>0.01</td>
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<tr>
<td>Distal control vs distal large/massive</td>
<td>94.83 vs 44.40</td>
<td>0.02</td>
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<tr>
<td>Distal small/medium vs distal large/massive</td>
<td>65.60 vs 44.40</td>
<td>0.4</td>
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</table>
ence for and against it. Our findings suggest that excision of a portion of distal tissue in a larger tear is unlikely to be detrimental to the repair, since the tissue is often of poor quality. Repair of the tendon using tissue of better quality more proximally once the distal tissue has been excised, or advancement of better tissue to produce a 'foot-print type' repair as described by Lo and Burkhart, may be more advantageous.

There appeared to be little difference in quality when comparing proximal tissue in the smaller tears with the corresponding control tissue. This may be, in part, the reason for the higher rate of integrity of repair seen in such lesions when compared with larger tears, and supports the widely held view that torn tendons begin as small lesions and ultimately progress to massive tears.

Variation was seen in the results, with some of the smaller tears showing poorer cellular activity, particularly in their distal tissue, when compared with the corresponding tissue in larger tears. Conversely, some of the larger tears had good cellular activity, particularly when compared with similarly sized tears. Increasing tear size appears to be synonymous with deteriorating tissue, but our study indicated that there were exceptions and that size did not necessarily equate to the physiological capability of a torn tendon. Gazielli, Gleyze and Montagnon suggested that the quality of the tissue and not simply the size was a more important factor when predicting the outcome of surgical repair. It is likely that a small number of torn tendons which are denied repair because of their large size may have the physiological capability to heal. Conversely, some smaller tears, which are thought to be amenable to repair because of their superior prognosis and less technical demand, may not have an advantage. In the repair of massive tears, however, the tissue at the edge of the tear is essentially dead and will not heal, and even tissue 1.5 cm from the edge of the tear is of such poor viability that conventional repair is unlikely to be successful.

Supplementary Material
A further opinion by Professor G. Kontakis is available with the electronic version of this article on our website at www.jbjs.org.uk

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

References
5. Codman EA. The shoulder: rupture of the supraspinatus tendon and other lesions in or about the subacromial bursa. Boston: Thomas Todd, 1934.