

# Effects of Platelet-Rich Plasma and Indomethacin on Biomechanics of Rotator Cuff Repair

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## Abstract

We conducted a study to determine if platelet-rich plasma (PRP) enhances the strength of rotator cuff repair (RCR) and if concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs) affects PRP efficacy. We also wanted to determine the optimal centrifugation protocol for making PRP from rats.

This study used 48 rats, 14 in a centrifugation protocol and 34 in an operative protocol. Six syngeneic rats from the operative group were used as PRP blood donors; the other 28 operative rats underwent bilateral RCRs. The Autologous Conditioned Plasma system (Arthrex) was used to prepare leukocyte-poor PRP. One shoulder was randomized to an intratendinous PRP injection, and the other received normal saline. Each rat was also randomly placed on a postoperative diet, either a regular diet or an indomethacin-enhanced

diet. After rats were euthanized at 3 weeks, specimens were dissected to isolate the supraspinatus tendon at its humeral attachment, which was subjected to biomechanical testing.

PRP prepared with a protocol of 5 minutes  $\times$  1300 revolutions per minute had the highest platelet index. Mean (SD) energy to failure was significantly higher ( $P = .03$ ) in tendons treated with PRP, 11.7 (7.3) N-mm, than in tendons treated with saline, 8.7 (4.6) N-mm. Both groups (PRP, saline) showed no significant differences between tendons treated with NSAIDs and those not treated with NSAIDs.

Intraoperative application of PRP enhances energy to failure after RCR in rats. There were no differences in biomechanical strength with NSAID use and no interactions between PRP and NSAID use.

**R**otator cuff tears are a common source of shoulder pain and disability among older adults and athletes. Full-thickness tears alone occur in up to 30% of adults older than 60

years.<sup>1</sup> Surgical repair is plagued by an unpredictable rate of recurrence (range, 11%-94%).<sup>1-10</sup> As a result of improved suture materials, knotting patterns, and anchor designs, hardware issues are no longer the primary cause of rotator cuff repair (RCR) failures; now the principal mode of failure is biologic.<sup>2</sup> Animal model studies have found that, after injury and subsequent healing, the tendon-bone interface remains abnormal.<sup>11</sup> Rotator cuff research therefore has focused largely on biological enhancement of tendon-to-bone healing.

One means of biological augmentation is autologous platelet-rich plasma (PRP), which has supraphysiologic concentrations of platelets and their secreted growth factors. Although there is no consensus on the long-term efficacy of PRP, some studies suggest PRP accelerates healing over short and intermediate terms, which may contribute to

## Take-Home Points

- The optimal centrifugation protocol for production of rat PRP is 1300 rpm for 5 minutes.
- PRP administration in RCR improves tendon biomechanics in a rat model.
- Administration of NSAIDs following RCR has no significant effect on tendon biomechanical properties.
- NSAIDs may be co-administered with PRP without reducing efficacy of PRP.
- The role of PRP and NSAIDs in human RCR remains unclear.

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a more rapid decrease in pain and more rapid return to normal activities.<sup>12-18</sup>

Similarly, systemic nonsteroidal anti-inflammatory drugs (NSAIDs) have long been used to treat musculoskeletal injuries, including rotator cuff pathology. However, NSAIDs inhibit cyclooxygenase activity, and clinical and experimental data have shown that cyclooxygenase 2 function is crucial in normal tendon-to-bone healing.<sup>19-21</sup>

Comprehensive studies have been conducted on the efficacy of both PRP and NSAIDs, but the interaction of concurrently used PRP and NSAIDs has not been determined. As many physicians use both modalities in the treatment of soft-tissue injuries, it is important to study the potential interactions when coadministered. Prior studies in small animal models suggest NSAIDs may impair tendon-to-bone healing in RCR, but there is no evidence regarding the effect of NSAIDs on the efficacy of PRP treatment.<sup>21</sup>

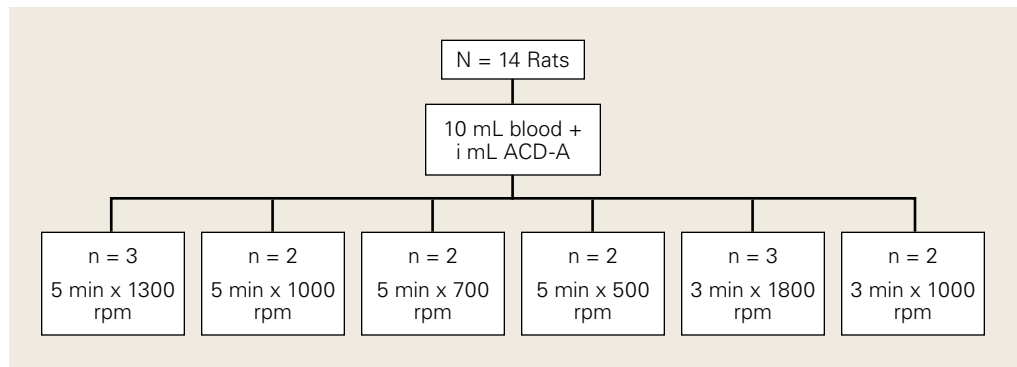
We conducted a study to determine the interaction of PRP and NSAIDs when used as adjuncts to RCR in a rat model. We hypothesized that PRP would increase the strength of RCR and that NSAIDs would interfere with the effects of PRP. A preliminary study objective was to determine an appropriate centrifugation protocol for producing PRP from rat blood, for use in this study and in future rat-based studies of PRP.

## Materials and Methods

### Part A: Pretesting Determination of PRP

#### Centrifugation Protocol

Fourteen adult male Fischer rats were used in part A of this study, which was conducted to determine an appropriate PRP centrifugation protocol. Traditional PRP centrifugation protocols are established for human blood, but rat red blood cells (RBCs) and human RBCs differ in size.<sup>22</sup> In our preliminary study, we wanted to determine the adjusted centrifuge speed and duration for producing clinically optimal PRP from rats. Clinically optimal PRP has reduced levels of RBCs, which decrease platelet affinity. Although the role of leukocytes in PRP preparations is debated, reducing the number of white blood cells (WBCs) decreases the number



**Figure 1. Part A of this study: 6 different centrifugation protocols.**  
Abbreviations: ACD-A, acid citrate dextrose solution A; rpm, revolutions per minute.

of matrix metalloproteinases and reactive oxygen species that may lead to inflammation. We used the platelet index (ratio of platelets to WBCs) and the RBC count to quantify the quality of our PRP sample.

Each rat in part A was anesthetized while supine. We used the Autologous Conditioned Plasma (ACP) system (Arthrex), which requires only 1 centrifugation cycle to create PRP. About 9 mL or 10 mL of blood was obtained by cardiac aspiration using an ACP Double Syringe (Arthrex). After blood retrieval, a thoracotomy was performed to confirm each rat's death.

Each blood sample was centrifuged once under 1 of 6 different centrifugation protocols, varying in duration (minutes) and speed (revolutions per minute [rpm]) (**Figure 1**). Initially, 12 rats were evenly divided among the 6 protocols, 2 rats per group. The spun PRP product from each rat was evaluated for RBC count, platelet count, and WBC count, and a platelet index was calculated. The 2 centrifugation protocols with the highest mean platelet index, 5 minutes  $\times$  1300 rpm and 3 minutes  $\times$  1800 rpm, were then increased in size by 1 rat each (new sample size, 3). With these 2 rats added, the highest overall platelet index and lowest RBC and WBC counts were found in the 5 minutes  $\times$  1300 rpm protocol (**Table 1**). We concluded that this protocol produces optimal PRP from rats, and it was implemented for use in part B of the study.

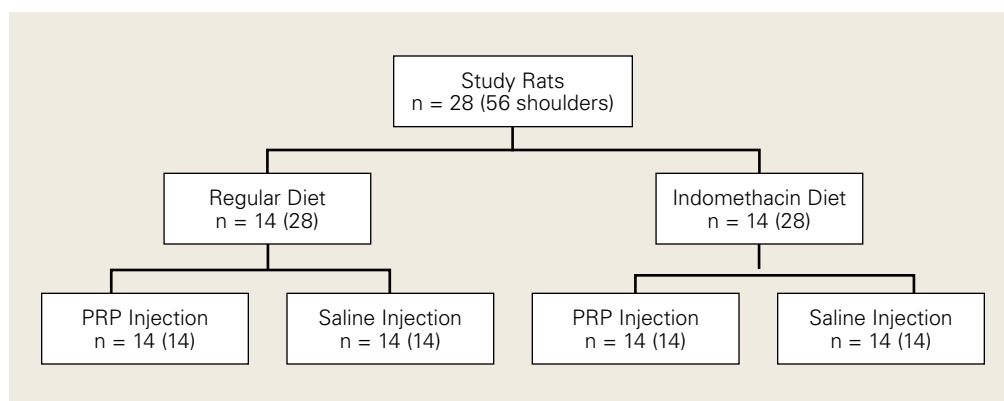
### Part B: Determining the Effects of PRP and NSAIDs on RCR in a Rat Model

**Operative Cohort.** Of the 34 Fischer rats used in part B of this study, 6 were used as blood donors for PRP production, and the other 28 underwent bilateral rotator cuff surgeries. We used donor rats to maximize the amount of PRP retrieval, allocat-

**Table 1. Part A: Determination of Appropriate Centrifugation Protocol in Rats**

Centrifugation Time, min	Speed, rpm	n	Red Blood Cells, $\times 10^3/\mu\text{L}$	Platelets, $\times 10^2/\mu\text{L}$	White Blood Cells, $\times 10^3/\mu\text{L}$	Platelet Index
5	1300	3	0.03	699.2	0.2	3811.6
5	1000	2	0.2	851.4	1.6	535.9
5	700	2	2.6	588.6	1.5	354.2
5	500	2	5.0	873.5	6.6	135.9
3	1800	3	0.2	494.8	0.6	2511.4
3	1000	2	3.1	1221.7	4.2	298.3

Abbreviation: rpm, revolutions per minute.



**Figure 2.** Organization of operative study cohorts.  
Abbreviation: PRP, platelet-rich plasma.

ing about 1 donor rat per 5 operative rats. Fischer rats are an inbred strain, so the PRP from a donor Fischer rat simulates autologous blood in other Fischer rats. Use of allogenic blood is consistent with prior rat PRP studies.<sup>23,24</sup>

**Operative Technique.** Each bilateral surgery was performed by a single board-certified shoulder surgeon, and the anesthetic and surgical protocols were followed as approved by the home institution's Institutional Animal Care and Use Committee. Before surgery, blood was harvested for PRP production from donor rats, as described earlier, and centrifuged for 5 minutes  $\times$  1300 rpm. After anesthetic induction and skin incision, the deltoid muscle was cut to expose the acromion and underlying rotator cuff. The distal supraspinatus tendon was sharply detached from the greater tuberosity. A bone-tunnel RCR was performed by drilling a transverse tunnel across the greater tuberosity and affixing the tendon to its footprint with a 5-0 polypropylene suture (Prolene; Ethicon). Each

rat was then randomly assigned to receive 50  $\mu\text{L}$  of donor PRP injected in 1 operative shoulder and saline in the contralateral shoulder. Injections were made in the supraspinatus tendon at its attachment to the humerus. Deltoid and skin were closed with 4-0 polyglactin (Vicryl) suture (Ethicon) and staples, respectively.

**Postoperative Protocol.**

After surgery, the rats were allowed regular am-

bulation and feeding. The first 2 weeks after surgery, 14 rats were fed a regular diet, and the other 14 an indomethacin-based diet. Other studies have found that rats do not prefer one diet over the other.<sup>20</sup> The 56 shoulders were divided into 4 treatment-diet cohorts (PRP-NSAIDs, saline-NSAIDs, PRP-regular, saline-regular) (Figure 2). Rat weights were monitored daily for the first 5 days and twice weekly thereafter. Indomethacin was administered at a dose of 3 mg/kg/d by infusion in a dry food pellet, and excess food was weighed before the next feeding to quantify drug intake.<sup>21</sup> After 14 days, the indomethacin-based diet was changed to a control diet for another 7 days. The rats in the regular-diet group received a control diet all 21 days. All rats were euthanized 3 weeks after surgery, a time point used in previous studies.<sup>24,25</sup>

**Tendon Preparation.** Immediately post mortem, each shoulder was grossly dissected to isolate the supraspinatus muscle attached to the humerus. Shoulders were then frozen in 0.15-M saline solu-

tion until specified biomechanical testing dates.

On day of dimensional/biomechanical testing, each specimen was thawed at room temperature and finely dissected under a microscope (Stemi 200-C; Car Zeiss). After dissection, the humeral shaft was embedded in polymethylmethacrylate within a test tube. The free end of the supraspinatus tendon was glued within a "tab" of waterproofed emery cloth, leaving about 2 mm of tendon between the tab and the greater tuberosity.

**Dimensional Analysis.** Photographs were taken of each tendon under 0.2 N of tension to simulate the biomechanical preload (to be described). A Canon G9 digital camera attached to a microscope was used to photograph 2 dimensions: thickness (superoinferior) and width (anteroposterior). A 3-mm gauge block (Mitutoyo America) (Figures 3A-3C) was placed on all images, and ImageJ photoanalysis software (National Institutes of Health) was used to measure each dimension at 5 different points along the tendon. The mean of these 5 measurements represented the respective thickness or width, and the SD represented the measurement error. Statistical differences between treatments (PRP, saline) and diet (NSAIDs, regular) were assessed with 2-way

analysis of variance (ANOVA). Significance was set to an  $\alpha$  level of  $P < .05$ .

**Biomechanical Analysis.** A 5848 MicroTester (Instron) was used for biomechanical testing. Each tabbed tendon, held by a pneumatic clamp attached to the MicroTester, was tested in a preconditioning phase and then a ramp-to-failure phase. A constant drip of 0.15-M saline was run through the apparatus to simulate physiologic hydration of tissue. After the embedded specimen was secure within the loading apparatus, an initial tensile preload of 0.2 N was applied. After preloading, the tendon was run through a preconditioning phase to account for viscoelastic relaxation. Immediately after preconditioning, each tendon was subjected to failure testing at a ramp rate of 0.1 mm/s. Force data were collected as a function of displacement, allowing for the calculation of 4 biomechanical parameters: failure force, tendon stiffness and normalized stiffness, energy to failure, and total energy. Tendon stiffness is the



**Figure 3.** (A) Supraspinatus tendon under a 0.2-N tare with a 3-mm gauge block. (B) Humeral shaft embedded in polymethylmethacrylate with the head protruding outward and secured by the plate. (C) In biomechanical testing setup, the tube is angled 15° from vertical, which simulates 105° of shoulder abduction. The shoulder is continuously bathed with a 0.15-M saline.

**Table 2. Comparison of Dimensional Measurements in 4 Diet-Treatment Cohorts**

Measurement, mm	Diet-Treatment Cohort							
	NSAID/No PRP		NSAID/PRP		No NSAID/No PRP		No NSAID/PRP	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Width	4.6	0.5	4.2	0.4	4.1	0.4	4.2	0.6
Thickness	1.8	0.3	2.0	0.6	1.8	0.3	1.9	0.3
Length	7.3	0.6	7.1	0.5	7.0	0.8	7.4	0.4
Measurement, mm	PRP		No PRP		NSAID		No NSAID	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
	Width	4.2	0.5	4.4	0.5	4.4	0.5	4.2
Thickness	1.9	0.5	1.8	0.3	1.9	0.5	1.8	0.3
Length	7.2	0.5	7.1	0.7	7.2	0.6	7.2	0.6

Abbreviations: NSAID, nonsteroidal anti-inflammatory drug; PRP, platelet-rich plasma.

slope of a curve-fit line of the initial peak; failure force is the force of the highest peak; energy to failure is the area under the curve (AUC) to the highest peak; and total energy is the AUC from the start of failure ramping to the point at which the tendon is torn off completely. Two-way ANOVA was used to assess the differences between treatment groups and diet groups for all parameters. Statistical significance was set at  $P < .05$ .

A power analysis was performed to determine ability to detect differences between cohorts. For power of 80% and  $P = .05$ , a difference of 16% of the mean could be detected for failure force, 30% for energy to failure, 14% for total energy to failure, and 24% for stiffness. In addition, a difference of 4% of the mean could be detected for tendon length, 6% for width, and 10% for thickness.

## Results

There were no significant differences in supraspinatus width, thickness, or length between

treatments or diet types (Table 2).

Tendon mode of failure was consistent throughout testing. All 56 shoulders failed at the humeral attachment/tendon insertion. Nine of the 56 experienced partial failure at the attachment combined with partial failure in the midsubstance region.

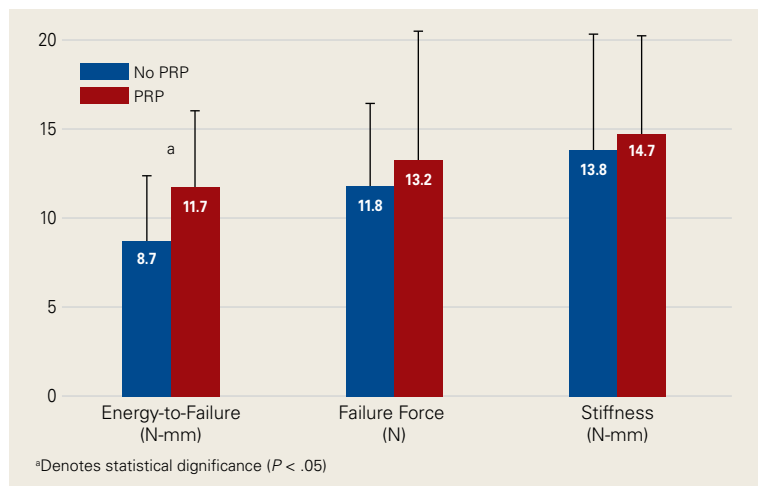
Across all collective treatment-diet groups and biomechanical parameters, there was only 1 statistically significant difference. Mean (SD) energy to failure was significantly higher ( $P = .03$ ) in shoulders treated with PRP, 11.7 (7.3) N-mm, than in those treated without PRP, 8.7 (4.6) N-mm (Figure 4). There were no statistically significant differences between shoulders treated with indomethacin and those treated without indomethacin (Table 3), and no statistically significant relationships between treatment and drug for any other biomechanical parameter (Figures 5-7).

## Discussion

Our preliminary objective in this study was to determine the optimal centrifugation protocol for producing rat-based PRP. Optimal PRP requires a dense concentration of platelets as well as reduced levels of RBCs and WBCs.<sup>25</sup> We used the platelet index to quantify the quality of our PRP samples, and we obtained the highest platelet index for the protocol of 5 minutes  $\times$  1300 rpm. This finding may be useful in later rat studies involving PRP.

The primary objective of this study was to assess the effect of the interaction of PRP and NSAIDs on RCR. PRP has been found to augment RCR,<sup>12,26,27</sup> but indomethacin may impair healing.<sup>21,25</sup> We hypothesized that shoulders treated with PRP would have more biomechanical strength than control shoulders and that indomethacin would decrease biomechanical strength.

Our data showed increased energy to failure of the rotator cuff with PRP injections ( $P = .03$ ). All other biomechanical parameters showed no



**Figure 4.** Biomechanical parameters comparing platelet-rich plasma (PRP) and non-PRP treatment shoulders.

\*Energy-to-failure, no PRP  $<$  PRP ( $P = .03$ ); failure force, no PRP vs PRP ( $P = .65$ ); stiffness, no PRP vs PRP ( $P = .53$ ). Error bars indicate 1 SD.

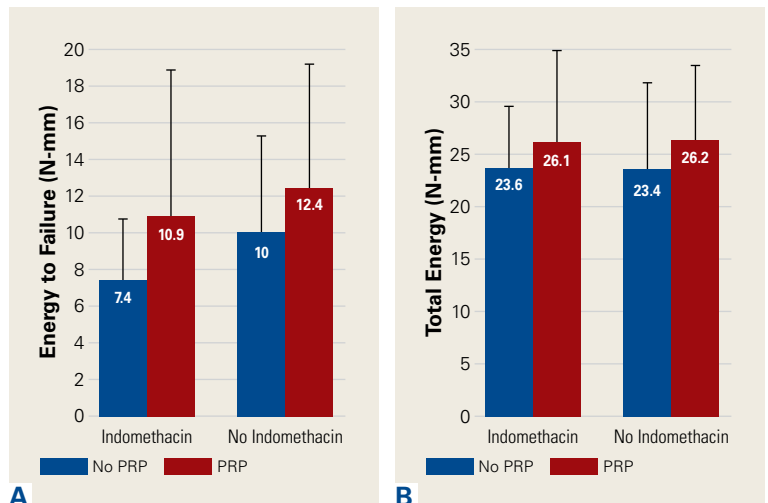
**Table 3. Comparison of Biomechanical Parameters in 2 Diet Cohorts (n = 28 in Each Cohort)**

Biomechanical Parameter	No Indomethacin		Indomethacin		P
	Mean	SD	Mean	SD	
Failure force, N	12.7	3.8	12.2	4.3	.65
Energy-to-failure, N-mm	9.2	6.3	11.2	6.1	.30
Energy to complete rupture, N-mm	24.8	7.7	24.8	7.4	.99
Stiffness, N-mm	14.8	5.9	13.7	6.2	.57

significant differences with PRP treatment, though there were statistically insignificant trends of increased total energy, failure force, and stiffness in the PRP cohorts. There were no statistically significant differences between the indomethacin and no-indomethacin groups, and indomethacin had no effect on the efficacy of PRP treatment. It should be noted that the measurements of total energy, energy to failure, and failure force best reflect the strength of the tendon–bone interface. Other biomechanical measures, such as stiffness and normalized stiffness, are physical properties of the tendon itself and apply less to enthesis strength, which was the primary focus of this study.

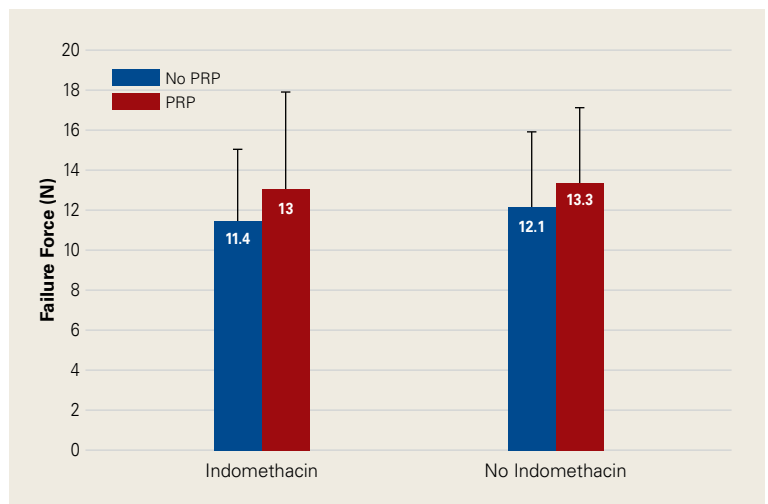
Beck and colleagues<sup>23</sup> studied the effect of allogeneic PRP on RCR in a rat model. They tested biomechanical and histologic outcomes 7, 14, and 21 days after surgery. There was no significant difference in failure load between the 2 groups at any time point. Compared with failure strain in the control group, failure strain in the PRP group was decreased at 7 days, normalized at 14 days, and increased at 21 days. The authors hypothesized that increased tendon failure strain at 21 days may have reduced forces being transmitted to the suture fixation site, which may be clinically significant and warrants further investigation. In a similar study, by Dolkart and colleagues,<sup>28</sup> intraoperative PRP administration enhanced the maximal load-to-failure and stiffness of rats' repaired rotator cuffs. On histologic examination, tendons treated with PRP (vs control tendons) had more organized collagen. Although these studies have limitations similar to our study, these results further support improved tendon-to-bone healing with PRP.

In clinical application, Barber and colleagues<sup>26</sup> found that, compared with controls, suturing PRP fibrin matrix into the rotator cuff during repair decreased the incidence of magnetic resonance imaging–detected retears. However, in 2 prospective, randomized trials, Castricini and colleagues<sup>29</sup> and Weber and colleagues<sup>30</sup> found that use of PRP in RCR did not improve outcomes. All 3 studies differ from ours in that they used fibrin matrix. However, Ersen and colleagues<sup>31</sup> found no difference in the effects of PRP on rotator cuff healing between injection and fibrin matrix; PRP improved biomechanical properties of repaired rotator cuff independent of administration method. In a meta-analysis of PRP supplementation in RCR, Warth and colleagues<sup>32</sup> found a statistically significant improvement in retear rates for tears >3 cm repaired with a double-row technique, but otherwise no overall im-



**Figure 5.** (A) Energy-to-failure comparing all treatment-diet cohorts. No PRP < PRP ( $P = .03$ ), NSAIDs vs no NSAIDs ( $P = .30$ ), treatment vs diet ( $P = .71$ ). (B) Total energy comparing all treatment-diet cohorts. No PRP vs PRP ( $P = .13$ ), NSAIDs vs no NSAIDs ( $P = .99$ ), treatment vs diet ( $P = .92$ ). Error bars indicate 1 SD.

Abbreviations: NSAID, nonsteroidal anti-inflammatory drug; PRP, platelet-rich plasma.

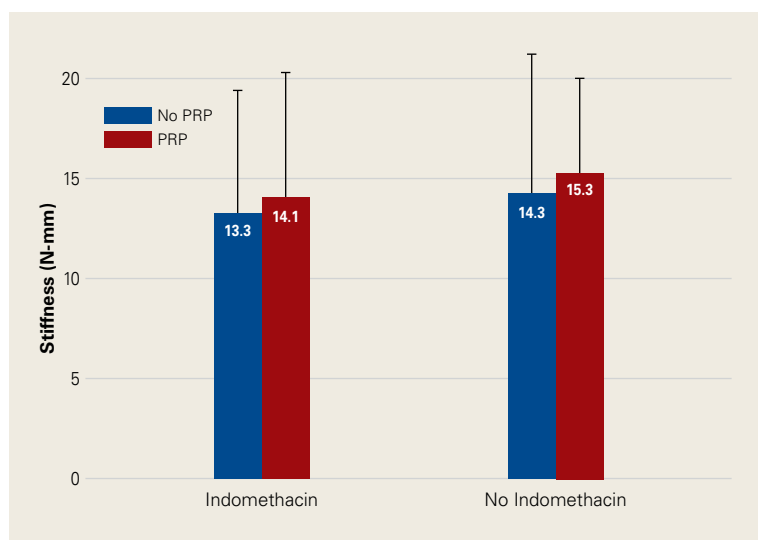


**Figure 6.** Failure force comparing all treatment-diet cohorts. No PRP vs PRP ( $P = .19$ ), NSAIDs vs no NSAIDs ( $P = .65$ ), treatment vs diet ( $P = .87$ ). Error bars indicate 1 SD.

Abbreviations: NSAID, nonsteroidal anti-inflammatory drug; PRP, platelet-rich plasma.

provement in retear rates or outcome scores with PRP. The authors acknowledged that the significant heterogeneity of the studies in their meta-analysis may have affected the quality of their data.

Although our study provides some insight into the effectiveness of PRP in tendon repair, the lack of standardization in PRP preparation and time points tested makes comparisons with similar studies difficult.<sup>33</sup> Recent reports have emphasized that not all PRP separation systems yield similar products.<sup>33</sup> Platelet concentrations, and therefore platelet-derived growth factor concentrations, differ between systems and may yield different clinical outcomes. Our decision to use leukocyte-reduced



**Figure 7.** Stiffness comparing all treatment-diet cohorts. No PRP vs PRP ( $P = .53$ ); NSAIDs vs no NSAIDs ( $P = .57$ ); treatment vs diet ( $P = .96$ ). Error bars indicate 1 SD. Abbreviations: NSAID, nonsteroidal anti-inflammatory drug; PRP, platelet-rich plasma.

PRP is supported by a meta-analysis by Riboh and colleagues,<sup>34</sup> who reviewed the literature on the effect of leukocyte concentration on the efficacy of PRP products. They found that, in the treatment of knee osteoarthritis, use of leukocyte-poor PRP resulted in improved functional outcomes scores in comparison with placebo, but this improvement did not occur with leukocyte-rich PRP. However, there is still no consensus on optimal preparation, dosing, and route of administration of PRP, and preparations described in the literature vary.

This study also assessed the interaction of PRP and NSAIDs. Although there were no statistically significant differences between treatment and diet, shoulders treated with indomethacin alone showed a trend toward weaker biomechanical parameters in comparison with shoulders treated with saline alone, with PRP alone, or with both PRP and indomethacin. A larger sample would be needed to establish statistical significance. These trends are not surprising, as Cohen and colleagues<sup>21</sup> found that NSAIDs, specifically indomethacin and celecoxib, significantly inhibited rotator cuff tendon-to-bone healing. The authors also found that a 2-week course of indomethacin was sufficient to significantly inhibit tendon-to-bone healing. In fact, although the drugs were discontinued after 14 days, biomechanical properties were negatively affected up to 8 weeks after repair. Our results differ from theirs even though the 2 studies used similar doses and administration protocols.

One strength of this study was that all surgeries were performed by a single board-certified surgeon using a standardized technique. In addition,

a control group was established, and personnel and techniques for all fine dissections and biomechanical tests were consistent throughout. Blinded randomization and diet normalization, as well as adequate power for detecting significant effects, strengthened the study as well.

The study had several limitations. First, whereas most human rotator cuff tears are chronic, we used a model of acute injury and repair. As acute tears that are immediately repaired are more likely to heal, detection of differences between cohorts is less likely. However, using an acute model is still the most reliable strategy for inducing a controlled injury with reproducible severity. Second, we analyzed data at only 1 time point, which may not provide an accurate representation of long-term effects. Third, systemic administration of indomethacin did not allow for intra-rat shoulder comparisons of the different drug groups. Fourth, although it is possible that the dosage of NSAID was insufficient to produce significant differences in biomechanics, our dosage was consistent with that used in a study that found a significant effect on tendon healing.<sup>21</sup>

## Conclusion

Our study found that the strength of the supraspinatus tendon enthesis as defined by energy to failure was increased with intratendinous PRP injection. Indomethacin showed no statistical effect, but there was a trend toward reduced strength after repair. However, the extent to which coadministration of indomethacin affects PRP remains unclear, and these data cannot necessarily be extrapolated to the typical human rotator cuff tear caused by chronic repetitive stress.

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*This paper will be judged for the Resident Writer's Award.*