

# Bilateral posterior cervical cages provide biomechanical stability: assessment of stand-alone and supplemental fixation for anterior cervical discectomy and fusion

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**Introduction:** Supplemental posterior instrumentation has been widely used to enhance stability and improve fusion rates in higher risk patients undergoing anterior cervical discectomy and fusion (ACDF). These typically involve posterior lateral mass or pedicle screw fixation with significant inherent risks and morbidities. More recently, cervical cages placed bilaterally between the facet joints (posterior cervical cages) have been used as a less disruptive alternative for posterior fixation. The purpose of this study was to compare the stability achieved by both posterior cages and ACDF at a single motion segment and determine the stability achieved with posterior cervical cages used as an adjunct to single- and multilevel ACDF.

**Methods:** Seven cadaveric cervical spine (C2–T1) specimens were tested in the following sequence: intact, C5–C6 bilateral posterior cages, C6–C7 plated ACDF with and without posterior cages, and C3–C5 plated ACDF with and without posterior cages. Range of motion in flexion–extension, lateral bending, and axial rotation was measured for each condition under moment loading up to  $\pm 1.5$  Nm.

**Results:** All fusion constructs significantly reduced the range of motion compared to intact in flexion–extension, lateral bending, and axial rotation ( $P < 0.05$ ). Similar stability was achieved with bilateral posterior cages and plated ACDF at a single level. Posterior cages, when placed as an adjunct to ACDF, further reduced range of motion in both single- and multilevel constructs ( $P < 0.05$ ).

**Conclusion:** The biomechanical effectiveness of bilateral posterior cages in limiting cervical segmental motion is comparable to single-level plated ACDF. Furthermore, supplementation of single- and multilevel ACDF with posterior cervical cages provided a significant increase in stability and therefore may be a potential, minimally disruptive option for supplemental fixation for improving ACDF fusion rates.

**Keywords:** cervical spine, posterior fusion, biomechanics, cervical facets, DTRAX Posterior Cervical Cage

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## Introduction

Anterior cervical discectomy and fusion (ACDF) is commonly performed to treat one- and two-level cervical spondylosis. Favorable fusion rates have been reported; nonunion rate is ~4% for single level plated ACDF with allograft.<sup>1,2</sup> However, fusion success declines with the number of treated levels.<sup>3</sup> Reported pseudarthrosis rates are as high as 18% and 37%, in two- and three-level ACDF constructs, respectively.<sup>1,4,5</sup> To achieve solid bony fusion, both a favorable bone healing environment and mechanical stability are required.<sup>6</sup> These conditions become especially important in patients undergoing multilevel fusion in whom the risk of pseudarthrosis and revision surgery is more prevalent.<sup>7</sup>

Fusion constructs using ACDF supplemented with posterior fixation are more stable and have been shown to improve fusion rates.<sup>8,9</sup> The most commonly used implants, lateral mass screw/rod constructs and transfacet screws, provide effective stabilization, but typically require an open posterior approach with considerable muscle retraction, which has been shown to be associated with significant blood loss, postoperative pain, and morbidity.<sup>7,9–13</sup> Fusion with expandable posterior cervical cages placed between the facet joints has been described for the treatment of radiculopathy with favorable results at 1 year.<sup>14,15</sup> Bilateral placement of similar devices have been shown to decrease the range of motion (ROM) at the index level, increase foraminal area, and preserve cervical lordosis.<sup>16–19</sup>

More recently, a nonexpandable titanium alloy posterior cervical cage has become available (DTRAX Posterior Cervical Cage, Providence Medical Technology, Walnut Creek, CA, USA).<sup>15,20</sup> To date, no studies have evaluated the biomechanical effects of this cage compared to ACDF or assessed their contribution to stability when used as supplemental posterior fixation in plated ACDF procedures.

This study tested the following hypotheses:

1. Effectiveness of the DTRAX Posterior Cervical Cage stabilization in limiting motions in flexion–extension (FE), lateral bending (LB), and axial rotation (AR) will be comparable to that of an ACDF construct for a single-level fusion.
2. Supplemental posterior stabilization will significantly increase the effectiveness of the ACDF construct in single- and two-level settings.

## Methods

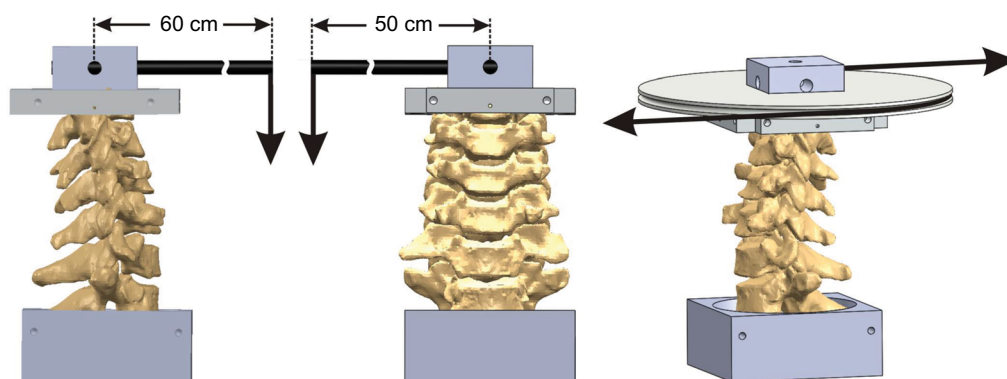
Seven fresh-frozen cadaveric cervical (C2–T1) spine specimens were acquired from an accredited tissue bank. This biomechanical study utilized human cadaveric tissue. While institutional review board approval was not necessary, approval was obtained from the Research and Development

committee at the Edward Hines Jr VA Hospital, where testing was performed. Specimen mean age (standard deviation) was  $41.1 \pm 9.1$  years (three male, four female). All specimens were free from osseous abnormalities and previous cervical spinal surgery. After the skin and paravertebral muscles were dissected, individual specimens were potted in aluminum cups with polymethyl methacrylate bone cement. Each specimen was fixed to a kinematic testing apparatus at the caudal end only; the cephalad end was left unconstrained.<sup>21,22</sup>

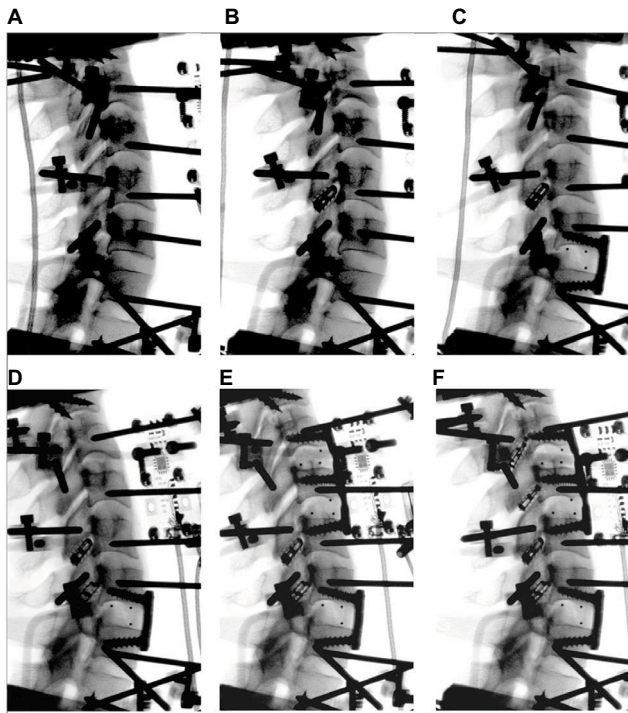
The testing apparatus allowed continuous cycling of the specimen between specified maximum moment endpoints ( $\pm 1.5$  Nm) in flexion, extension, LB, and AR. Specimens were subjected to quasi-static flexibility testing at a loading rate of 2.5 Nm/min. The angular motions of the C2 to C7 vertebrae relative to T1 were measured using an optoelectronic motion measurement system (Optotrak<sup>®</sup> Certus, Northern Digital, Waterloo, Canada). Testing was performed in moment control mode by placing a six-component load cell (Model MC3A-6-1000, AMTI Inc., Newton, MA, USA) under the specimen to measure the applied moments. Continuous loading in each of the three planes of motion was performed. Load-displacement data were collected until two reproducible load-displacement cycles were obtained.

Moment loading in FE and LB was performed using a force applied using a moment arm, while in AR a force couple was used to apply a pure moment (Figure 1). The moment arm length was 50 cm for LB and 60 cm for FE. Due to these long moment arms, the compressive load required to reach 1.5 Nm was  $\sim 2.7$  N in FE and 3.0 N in LB. Off-axis moments in all tests averaged less than 0.1 Nm. Fluoroscopic imaging (GE OEC 9800 Plus) was used to document implant placement.

Each of the seven specimens was tested sequentially in the following six conditions: 1) intact (C2–T1), 2) C5–C6 bilateral posterior cages, 3) C6–C7 plated ACDF, 4) C6–C7 plated ACDF + C6–C7 bilateral posterior cages, 5)



**Figure 1** Schematic of the loading apparatus for flexibility testing in flexion–extension (left image), lateral bending (center image), and axial rotation (right image).



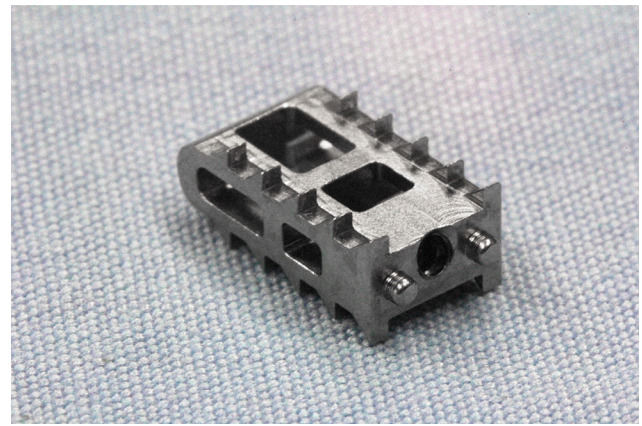
**Figure 2** Testing protocol.

**Note:** (A) Intact, (B) bilateral posterior cervical cages at C5–C6, (C) plated ACDF at C6–C7, (D) addition of posterior bilateral cervical cages at C6–C7, (E) plated ACDF at C3–C5, and (F) bilateral posterior cervical cages at C3–C4 and C4–C5.

**Abbreviation:** ACDF, anterior cervical discectomy and fusion.

C3–C5 plated ACDF, and 6) C3–C5 plated ACDF + C3–C5 bilateral posterior cages (Figure 2). This complex study design was intended to fully utilize the donated cadaveric tissue in order to investigate the effectiveness of the implants both in a stand-alone environment as well as in combination for single and two-level fusion constructs. A fluoroscopically guided posterior approach was used to place cages bilaterally between the cervical facet joints of the target level according to the manufacturer's surgical technique (Figure 3).<sup>23</sup> ACDF was performed according to standard surgical procedure. After discectomy, a 5 mm intervertebral cage was inserted and an anterior locking semiconstrained plate was applied (DePuy Synthes, Raynham, MA, USA).

Segmental ROM was analyzed using paired *t*-tests with Bonferroni correction for multiple comparisons. Significance level was set to  $\alpha = 0.05$ . The following four comparisons were conducted: intact versus C5–C6 cages, C5–C6 cages versus C6–C7 ACDF, C6–C7 ACDF versus ACDF + cages, and C3–C5 ACDF versus ACDF + cages. A stabilization intervention at any level is likely to alter ROM from intact conditions at subsequent spinal levels. Therefore, ROM values after each sequential step were compared to the ROM at that level during the previous protocol step. For example, the C6–C7 ROM after the ACDF (protocol step 3) was



**Figure 3** DTRAX Posterior Cervical Cage.

**Note:** The cervical cages are manufactured from implant grade titanium alloy (6Al-4V ELI Titanium) and each cage is 10 mm in length, 5.5 mm in width, and 2.5 mm in height.

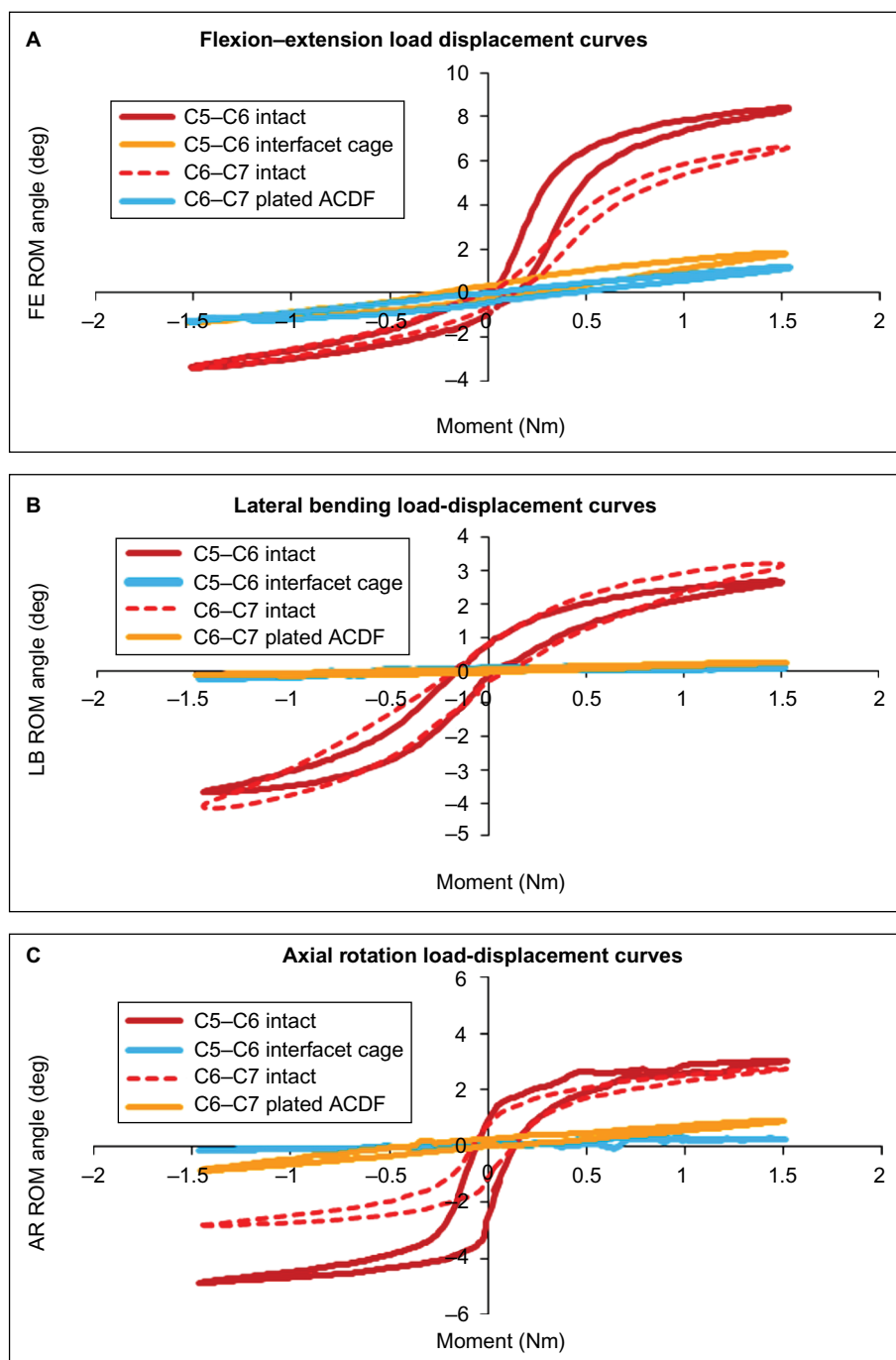
compared to the C6–C7 ROM after C5–C6 cages (protocol step 2) rather than the intact C6–C7 ROM from step 1. All comparisons were done separately for FE, LB, and AR, as no comparisons across load-types were intended. The statistical data analyses were performed with the use of the Systat 10.2 software package (Systat Software, Richmond, CA, USA).

## Results

The load-displacement curves of both the C5–C6 and C6–C7 levels after instrumentation with ACDF and bilateral posterior cervical cages can be well approximated by straight lines in all three loading modes (Figure 4). As the relationship between angular motion and the moment curve after instrumentation is nearly linear, the stiffness of the segment is equal to the maximum moment divided by the ROM. Thus, the assumption can be made that postinstrumentation comparison of ROM at maximum moments used in the current study is equivalent to comparing segmental stiffness. Assessment of fusion in the clinical setting is determined by ROM measurements, for example, on FE X-ray images, rather than stiffness calculations. Therefore, we report our results as ROM at the index levels for each tested condition.

## Comparison of posterior cervical cages and ACDF constructs

Posterior stabilization with bilateral cervical cages at C5–C6 significantly reduced the ROM in all directions when compared to the intact condition:  $10.7^\circ \pm 2.6^\circ$  to  $2.5^\circ \pm 1.3^\circ$  in FE,  $6.7^\circ \pm 2.8^\circ$  to  $0.4^\circ \pm 0.3^\circ$  in LB, and  $7.9^\circ \pm 2.8^\circ$  to  $1.1^\circ \pm 1.7^\circ$  in AR ( $P < 0.05$ ) (Table 1). Plated ACDF at C6–C7 significantly reduced ROM at the treated level compared to the preoperative ROM:  $12.3^\circ \pm 2.5^\circ$  to  $2.5^\circ \pm 0.8^\circ$  in FE,  $8.9^\circ \pm 1.5^\circ$  to  $1.6^\circ \pm 0.7^\circ$  in



**Figure 4** ROM curves with 0 N preload: (A) FE, (B) LB, and (C) AR.

**Abbreviations:** ACDF, anterior cervical discectomy and fusion; AR, axial rotation; FE, flexion-extension; LB, lateral bending; ROM, range of motion.

LB, and  $7.1^{\circ} \pm 1.2^{\circ}$  to  $1.7^{\circ} \pm 0.4^{\circ}$  in AR (all  $P < 0.05$ ) (Table 1). A statistical analysis comparing posterior cages at C5–C6 and ACDF at C6–C7 revealed no implant group effect for changes in ROM; a similar reduction in ROM was observed in each direction (FE, LB, and AR) for both constructs. However, the percent decreases in LB and AR were larger for the posterior cages compared to ACDF (LB:  $-94\% \pm 3.4\%$  vs  $-82\% \pm 6.1\%$ , AR:  $-87.2\% \pm 17.8\%$  vs  $-75.7\% \pm 7.1\%$ ).

### ACDF with supplemental fixation

Plated ACDF at C6–C7 significantly decreased ROM compared to intact in FE, LB, and AR (all  $P < 0.05$ ) (Table 1). ACDF supplemented with posterior cages further significantly reduced motion when compared to plated ACDF alone:  $2.5^{\circ} \pm 0.8^{\circ}$  to  $0.6^{\circ} \pm 0.3^{\circ}$  in FE,  $1.6^{\circ} \pm 0.7^{\circ}$  to  $0.1^{\circ} \pm 0.4^{\circ}$  in LB, and  $1.7^{\circ} \pm 0.4^{\circ}$  to  $0.2^{\circ} \pm 0.3^{\circ}$  in AR (all  $P < 0.005$ ) (Table 2).

**Table 1** Segmental ranges of motion in degrees, (mean  $\pm$  SD) for each condition under 0 N follower preload and 1.5 Nm moment for each test condition.

Testing mode	Intact	C5–C6 posterior cages	C6–C7 ACDF	C6–C7 ACDF + posterior cages	C3–C5 ACDF	C3–C5 ACDF + posterior cages
<b>C5–C6</b>						
Flexion–extension	10.7 $\pm$ 2.6	2.5 $\pm$ 1.3*	2.5 $\pm$ 1.2	2.5 $\pm$ 1.6	2.6 $\pm$ 1.7	2.5 $\pm$ 1.0
Lateral bending	6.7 $\pm$ 2.8	0.4 $\pm$ 0.3*	0.4 $\pm$ 0.4*	0.4 $\pm$ 0.4	0.5 $\pm$ 0.7	0.3 $\pm$ 0.1
Axial rotation	7.9 $\pm$ 2.8	1.1 $\pm$ 1.7*	0.6 $\pm$ 0.7*	0.5 $\pm$ 0.3	0.8 $\pm$ 1.3	0.6 $\pm$ 0.2
<b>C6–C7</b>						
Flexion–extension	11.4 $\pm$ 2.4	12.3 $\pm$ 2.5	2.5 $\pm$ 0.8*	0.6 $\pm$ –0.3*	0.6 $\pm$ 0.4	0.7 $\pm$ 0.4
Lateral bending	8.2 $\pm$ 1.7	8.9 $\pm$ 1.5	1.6 $\pm$ 0.7*	0.1 $\pm$ 0.4*	0.2 $\pm$ 0.3	0.1 $\pm$ 0.2
Axial rotation	7.5 $\pm$ 1.2	7.1 $\pm$ 1.2	1.7 $\pm$ 0.4*	0.2 $\pm$ 0.3*	0.0 $\pm$ 0.5	0.3 $\pm$ 0.2
<b>C3–C4</b>						
Flexion–extension	10.5 $\pm$ 5.1	11.6 $\pm$ 5.2	11.8 $\pm$ 5.4	12.1 $\pm$ 5.4	0.6 $\pm$ 0.4*	0.1 $\pm$ 0.1*
Lateral bending	13.7 $\pm$ 2.6	13.9 $\pm$ 2.7	15.2 $\pm$ 2.6	15.5 $\pm$ 2.6	0.9 $\pm$ 0.2*	0.1 $\pm$ 0.1*
Axial rotation	10.3 $\pm$ 1.5	10.7 $\pm$ 1.4	9.1 $\pm$ 1.8	9.6 $\pm$ 1.7	0.5 $\pm$ 0.5*	0.1 $\pm$ 0.2*
<b>C4–C5</b>						
Flexion–extension	11.3 $\pm$ 3.2	12.6 $\pm$ 3.1	12.8 $\pm$ 3.2	13.3 $\pm$ 3.1	1.1 $\pm$ 0.6*	0.2 $\pm$ 0.2*
Lateral bending	10.7 $\pm$ 2.4	10.8 $\pm$ 2.3	12.3 $\pm$ 2.4	12.0 $\pm$ 2.7	0.8 $\pm$ 0.5*	0.1 $\pm$ 0.1*
Axial rotation	12.1 $\pm$ 1.9	12.8 $\pm$ 1.9	11.6 $\pm$ 1.6	12.1 $\pm$ 1.7	1.6 $\pm$ 0.7*	0.1 $\pm$ 0.2*
<b>C3–C5</b>						
Flexion–extension	21.8 $\pm$ 7.9	24.2 $\pm$ 7.9	24.7 $\pm$ 8.2	25.4 $\pm$ 8.1	1.7 $\pm$ 0.9*	0.3 $\pm$ 0.2*
Lateral bending	24.4 $\pm$ 4.8	24.7 $\pm$ 4.9	27.5 $\pm$ 4.9	27.5 $\pm$ 5.1	1.7 $\pm$ 0.6*	0.2 $\pm$ 0.1*
Axial rotation	22.4 $\pm$ 2.5	23.6 $\pm$ 2.2	20.7 $\pm$ 2.2	21.7 $\pm$ 2.0	2.1 $\pm$ 0.5*	0.3 $\pm$ 0.2*

Note: \*Significantly different from baseline value (paired t-test,  $P < 0.05$ ).

Abbreviations: ACDF, anterior cervical discectomy and fusion; SD, standard deviation.

**Table 2** Effectiveness of posterior cervical cages as a supplement for single-level ACDF constructs

	ROM in degrees (mean $\pm$ SD) after single level C6–C7 instrumentation				
	Intact*	ACDF	Paired t-test, intact vs ACDF	ACDF + posterior cages	Paired t-test, ACDF vs ACDF + posterior cages
Flexion–extension	12.3 $\pm$ 2.5	2.5 $\pm$ 0.8	$P=0.000$	0.6 $\pm$ 0.3	$P=0.002$
Lateral bending	8.9 $\pm$ 1.5	1.6 $\pm$ 0.7	$P=0.000$	0.1 $\pm$ 0.4	$P=0.005$
Axial rotation	7.1 $\pm$ 1.2	1.7 $\pm$ 0.4	$P=0.000$	0.2 $\pm$ 0.3	$P=0.000$

Note: \*Intact represents baseline ROM values after posterior cage placement at C5–C6.

Abbreviations: ACDF, anterior cervical discectomy and fusion; ROM, range of motion.

In two-level fusion, plated ACDF alone significantly reduced ROM at C3–C5: values decreased from 25.4 $^{\circ}$  $\pm$ 8.1 $^{\circ}$  to 1.7 $^{\circ}$  $\pm$ 0.9 $^{\circ}$  in FE, 27.5 $^{\circ}$  $\pm$ 5.1 $^{\circ}$  to 1.7 $^{\circ}$  $\pm$ 0.6 $^{\circ}$  in LB, and 21.7 $^{\circ}$  $\pm$ 2.0 $^{\circ}$  to 2.1 $^{\circ}$  $\pm$ 0.5 $^{\circ}$  in AR (all  $P < 0.001$ ) (Table 3). Supplemental stabilization with the cages at C3–C5 further significantly reduced ROM when compared to plated ACDF alone: values decreased from 1.7 $^{\circ}$  $\pm$ 0.9 $^{\circ}$  to 0.3 $^{\circ}$  $\pm$ 0.2 $^{\circ}$  in FE, 1.7 $^{\circ}$  $\pm$ 0.6 $^{\circ}$  to 0.2 $^{\circ}$  $\pm$ 0.1 $^{\circ}$  in LB, and 2.1 $^{\circ}$  $\pm$ 0.5 $^{\circ}$  to 0.3 $^{\circ}$  $\pm$ 0.2 $^{\circ}$  in AR (all  $P < 0.05$ ) (Table 3).

## Discussion

The current study demonstrated that plated ACDF and bilateral posterior cages offer comparable postoperative segmental stability; both techniques significantly decreased cervical ROM in FE, LB, and AR. The percent reduction in LB and AR was higher for the posterior cage construct compared to the plated ACDF. This is likely due to the more lateral position

of the implants relative to the axis of rotation in LB and AR. The plated ACDF is closer to the axis of rotation and as such has a lesser ability to resist the LB and AR motions. Supplementation of one- and two-level plated ACDF constructs with bilateral posterior cervical cages further significantly decreased cervical ROM in all tested modes.

ACDF supplementation with transfacet screws was previously evaluated using a protocol similar to that reported herein.<sup>10</sup> Traynelis et al assessed FE, LB, and AR in eight cadaveric specimens before and after applying stand-alone plated ACDF and with the addition of unilateral and bilateral transfacet screws. Reported reduction in ROM values for the C6–C7 segment with concurrent bilateral transfacet screws is similar to those reported for posterior cages in the current study.

Kasliwal et al evaluated clinical and radiographic outcomes in patients who underwent revision surgery for

**Table 3** Effectiveness of posterior cervical cages as a supplement for two-level ACDF constructs

	ROM in degrees (mean $\pm$ SD) after two-level C3–C5 instrumentation				
	Intact	ACDF	Intact vs ACDF*	ACDF + cages	ACDF vs ACDF + cages*
<b>Flexion–extension</b>	25.4 $\pm$ 8.1	1.7 $\pm$ 0.9	<i>P</i> =0.000	0.3 $\pm$ 0.2	<i>P</i> =0.010
<b>Lateral bending</b>	27.5 $\pm$ 5.1	1.7 $\pm$ 0.6	<i>P</i> =0.000	0.2 $\pm$ 0.1	<i>P</i> =0.000
<b>Axial rotation</b>	21.7 $\pm$ 2.0	2.1 $\pm$ 0.5	<i>P</i> =0.000	0.3 $\pm$ 0.2	<i>P</i> =0.000

Note: \*Paired *t*-test.

Abbreviations: ACDF, anterior cervical discectomy and fusion; ROM, range of motion.

pseudarthrosis following ACDF using a cervical interfacet spacer similar to the device reported herein.<sup>24</sup> The authors report a 20-month follow-up on 19 patients. Patient-reported outcomes using Visual Analog Scale for neck and arm pain and Neck Disability Index showed significant improvement from baseline based on improvement of at least three points on Visual Analog Scale and 7.5 points on Neck Disability Index. There were no significant changes in cervical lordosis or C2–C7 sagittal vertical alignment.

One previous study analyzed the biomechanics of a construct similar in concept to the cages investigated in the current study. Leasure and Buckley evaluated foraminal decompression and segmental ROM after posterior bilateral placement of an expandable screw and washer system between the facet joints.<sup>16</sup> The results demonstrated a significant reduction in cervical ROM in flexion, LB, and AR after implantation. Although the implant design differed from the one evaluated in the current study, these results show that distracting and mechanically locking the translation of the interarticular facet surfaces relative to each other contribute to reduction of cervical segmental ROM.

As with all biomechanical cadaveric studies, this investigation has limitations. Notably, kinematic evaluation of the tested constructs provides evidence for the immediate postoperative effects of the implants and does not reflect the possible consequence of long-term cyclical loading experienced in vivo. Stand-alone constructs for ACDF and posterior cages were performed at different levels. C5–C6 and C6–C7 segments are similar in their intervertebral disc anatomy and facet morphologies. Their kinematic behavior is similar as evidenced by the intact ROM values of the two levels in FE, LB, and AR (FE: 10.7 vs 11.4, *P*=0.556; LB: 6.7 vs 8.2, *P*=0.235; AR: 7.9 vs 7.5, *P*=0.795). These two levels are a natural choice as controls for each other as they come from the same spine specimen and allow a paired comparison of construct data. Evaluating the two constructs at the same (C5–C6 or C6–C7) levels would have required a substantially larger number of specimens to account for the biologic variability between specimens. Furthermore, a sequential testing mode was employed in order to fully utilize each specimen.

When evaluating biomechanical results, it is important to note that kinematics vary depending on the cervical level and so comparisons are best made before and after surgeries at the same level.<sup>10</sup> The mean ROM in FE after the two-level fusion (C3–C5) was less than that of the mean single-level fusion at C6–C7. This was true for both ACDF and ACDF with posterior cages. This seemingly disparate result may be due to a combination of factors. As the FE testing was not performed using pure moments, C6–C7 could be subjected to a slightly higher (1.46 vs 1.5 Nm) moment than the upper cervical levels. However, a more likely explanation deals with differences in location of the segmental center of rotation (COR) and facet joints between the upper and lower cervical spines. The distance between the segmental COR and the fusion implant has a great effect on the stability provided by the implant. At C6–C7, the COR is positioned just posterior to the center of the upper endplate of C7 and coincident with the caudal surface of the interbody cage providing a poor mechanical advantage to resist FE motion. At C3–C4 and C4–C5, the COR is considerably more caudal providing improved mechanics for the ACDF to resist FE motion.<sup>25</sup>

As with any implant system, it is important to understand how sagittal alignment may be affected by the use of single and multilevel instrumentation. The focus of this study was evaluation of motion reduction with both posterior cervical cages and ACDF. As such, evaluation of sagittal alignment after each construct was beyond the scope of the study. Future analysis of biomechanical data and corroboration with clinical findings will provide insight into the effects of these fusion techniques on sagittal balance.

This study is the first to evaluate the role of bilateral cervical cages placed between the facet joints as a posterior supplement to plated ACDF at one and two levels. The results of the current study support the role of these implants to significantly increase stability in single and multilevel ACDF constructs. This suggests a role for the use of these implants when added stability is required, such as in situations in which ACDF has a higher risk of pseudarthrosis, or in the treatment of an established pseudarthrosis following ACDF.

## Conclusion

The biomechanical effectiveness of bilateral posterior cages in limiting cervical segmental motion is comparable to single-level plated ACDF. Supplementation of plated ACDF with these implants further increases cervical spine stability in single and multilevel ACDF constructs. These findings provide a biomechanical rationale for undertaking further studies to assess the performance of posterior cervical cages under repeated loading that simulates postoperative activity until biologic fusion occurs.

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## Disclosure

Dr Siemionow and Dr Phillips are consultants for Providence Medical Technology, and report no other conflicts of interest in this work. Dr Voronov, R Havey, G Carandang, and Dr Patwardhan report no conflicts of interest in this work, and had full control of all data.

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