Differentially Loaded Radiostereometric Analysis to Monitor Fracture Stiffness

A Feasibility Study

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Abstract Inability to accurately and objectively assess the mechanical properties of healing fractures in vivo hampers clinical fracture management and research. We describe a method to monitor fracture stiffness during healing in a clinical research setting by detecting changes in fracture displacement using radiostereometric analysis and simultaneously measuring applied axial loads. A method was developed for load application, positioning of the patient, and radiographic setup to establish the technique of differentially loaded radiostereometric analysis (DLRSA). A DLRSA examination consists of radiostereometric analysis radiographs taken without load (preload), under different increments of load, and without load (postload). Six patients with distal femur fractures had DLRSA examinations at 6, 12, 18, and 26 weeks postoperatively. The DLRSA method was feasible in a clinical setting. The method provides objective and quantifiable

data for internally fixed fractures and may be used in clinical research as a tool to monitor the in vivo stiffness of healing femoral fractures managed with nonrigid internal fixation.

Introduction

Traditionally, clinical assessment and conventional radiographs have been used to monitor fracture healing. Conventional radiographs identify the presence of mineralized callus tissue bridging the fracture site [29]. Identifying the number of cortices bridged by callus on conventional radiographs is the most reliable method of assessing the progression of healing in tibial fractures after intramedullary nailing [49]. However, although conventional radiographs give an indication of progress toward union, they are not sufficiently accurate to define an end point to healing of internally fixed fractures [15, 19, 29, 49]. Therefore, radiographs provide a limited and delayed surrogate for fracture healing and fail to allow early detection of delays or failures of union. Yet plain radiographs remain the standard tool for assessment of healing in human research studies investigating the effect new materials have on fracture repair [9, 20]. Without accurate and objective data for fracture healing in vivo, these studies will continue to rely on inaccurate and insensitive qualitative outcomes.

Fracture stiffness relates to the interfragmentary displacement in response to a given load. Numerous studies have concluded that monitoring stiffness is valuable for assessing fracture healing [10–12, 18, 34, 41]. Strain gauges attached to the pins of external fixators have been used to investigate interfragmentary displacement with time and under loading conditions [6, 13, 14, 23–25, 41, 48]. Some

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studies report the use of strain gauges on plates and nails to indirectly assess healing from the reduction in load through the fixation device [7, 8]. Although this technique yields useful information, bone movement is not measured directly and use of this technique is limited to fractures treated with external fixators. A technique is required that directly measures the mechanical properties of healing fractures and does not necessitate the use of specific fixation devices.

Radiostereometric analysis (RSA) is considered the most accurate radiographic method for measuring skeletal or implant movements *in vivo* [21]. It has been used predominantly in studies monitoring prosthesis migration and is considered the gold standard method [21, 22, 31, 36, 40, 42, 43, 46]. The method requires small tantalum markers to be inserted intraoperatively and two simultaneous radiographs taken over a calibration cage at selected times postoperatively. The radiation dose from RSA radiographs is 40% to 50% less than that from standard radiographs because only the dense tantalum markers need to be observed [21]. Measurement of interfragmentary displacement using high-resolution RSA is a potential method to study skeletal fracture healing patterns [21, 28]. The reported *in vitro* accuracy and precision of RSA measurements of radial fractures in each axis of movement is less than $\pm 30 \mu\text{m}$ for translations and $\pm 0.187^\circ$ for rotations [27]. The *in vitro* precision of RSA to monitor fragment motion in distal femoral fractures is less than $\pm 20 \mu\text{m}$ for translations and $\pm 0.15^\circ$ for rotations [16].

Clinical studies have used RSA to assess the position of specific fragments during the time of healing in ankle fractures [1–5], trochanteric fractures [17, 29, 30, 35–39], high tibial osteotomies [33], tibial plateau fractures [44], and radial fractures [26, 27]. For each of these studies, single RSA examinations were performed at prospective followups and interfragmentary displacement with time was measured. These studies were not designed to monitor fracture stability at any one time because they did not apply and measure load.

The only *in vivo* study in which RSA has been used to measure interfragmentary displacement under load is a case study of a tibia in a patient treated for leg lengthening using an Ilizarov external fixator [45]. In that case study, RSA radiographs were taken under one weightbearing load and axial displacement of the distal tibia was measured relative to the proximal tibia across the osteotomy site. To date, RSA with an applied axial load has been reported only in an *in vitro* study that compared interfragmentary displacements of three fixation methods for distal femur fractures [16].

Therefore, the aims of this study were to determine the feasibility of taking RSA radiographs while simultaneously applying axial load in a clinical setting and to apply this technique to monitor interfragmentary displacements under differential loads during healing.

Materials and Methods

To establish the feasibility of taking RSA radiographs while simultaneously applying axial load, the cases of six patients with distal femur fractures (AO fracture types 33 [32]) were investigated (Table 1). All patients were treated with periarticular locking plates (Synthes, Paoli, PA). We obtained ethics approval for this study from Royal Adelaide Hospital's Research Ethics Committee. All patients provided informed consent for insertion of tantalum markers during fracture fixation surgery and for the subsequent differentially loaded RSA (DLRSA) radiographic examinations.

We used a bead insertion gun (RSA Biomedical, Umeå, Sweden) to implant tantalum markers intraoperatively in the cortical or cancellous bone of each main fracture fragment proximal and distal to the fracture site. At least six markers were positioned to ensure they were optimally separated with respect to spatial orientation in each fracture fragment for each case. Adequate spatial positioning of beads was assessed using the condition number computed

Table 1. Clinical data for study patients

Patient	Age (years)	AO classification [32]	Comments
A	59	33A2	Pathologic fracture secondary to <i>Cryptococcus</i> osteomyelitis of the distal femur with extensive bone loss; revision surgery for nonunion
B	71	33B2	Complex triplanar intraarticular fracture with oblique pattern into lateral 2 cm of lateral femoral condyle; revision surgery for nonunion
C	62	33C2	Open fracture with secondary nonunion treated with bone grafting
D	60	33C2	Primary fixation for comminuted supracondylar fracture with midline vertical split into joint
E	80	33A3	Revision of fixation after failure of plate used to treat periprosthetic fracture above TKA (stable implant)
F	76	33A2	Primary fixation for highly comminuted periprosthetic fragility fracture above TKA (stable implant)

by the UmRSA[®] software output (Version 6.0; RSA Biomedical). The condition number has an inverse relationship to the distance of each bead from a central line in the fragment [22]. Therefore, as the spatial spread of beads increases, the condition number decreases. A condition number less than 150 is considered acceptable [47]. Additionally, through preoperative and intraoperative planning, we aimed to ensure that the beads were positioned sufficiently clear of the internal fixation to ensure adequate observation on both radiographs.

We modified the positioning of equipment for routine supine RSA radiographs to allow for standing weight-bearing RSA examinations of the lower limb (Fig. 1A). A room-mounted machine (Philips Bucky Diagnost, Eindhoven, The Netherlands) and mobile radiographic unit (Philips Practix 8000) were used to perform the radiographs. We mounted the RSA calibration cage (Uniplanar No. 43; RSA Biomedical) vertically with the cage's y axis positioned superiorly. The film-focus distance was 1.6 m and the tubes were angled 30° to each other. The digital images were processed, downloaded, and analyzed using UmRSA[®] software. We used exposure settings of 70 kVp and 10 mAs to observe the tantalum markers [22]. A customized patient lifter was designed to overcome limitations in the minimum height of the radiographic equipment (Fig. 1B). The platform of the lifter is large enough to allow a patient using a walking frame or crutches to step onto it before it is slowly raised to the required height.

Each DLRSA examination consisted of three to five pairs of RSA radiographs. We used a standing, weight-bearing position for each case. The force directed through the limb was assessed by digital scales positioned underneath the foot (Fig. 1B). We chose this method of load

application primarily to match current standard clinical practice in which patients are instructed to gauge their weightbearing status by reference to the load experienced by practicing on a bathroom scale. The first pair of radiographs was taken with the patient's foot lightly resting on the scales applying between 1 kg and 3 kg and thus not substantially loading the injured limb (preload RSA). We performed subsequent pairs of RSA radiographs in predominantly 20-kg increments up to the limit of 60 kg as defined by their clinical rehabilitation instructions. A tolerance of ± 1 kg was allowed around each loading increment. When the patient was unable to achieve a 20-kg multiple because of pain limitations, the maximum load to the nearest 10 kg was recorded. We performed a final pair of radiographs, again with the foot lightly resting on the scales (postload).

For each case, we performed DLRSA examinations at 6, 12, 18, and 26 weeks postoperatively. Each pair of radiographs taken under load and postload was directly compared with the reference preload radiographs. We recorded the interfragmentary displacements of each fracture in all six degrees of freedom. Mediolateral, proximodistal, and anteroposterior displacements relate to translations in the x, y, and z axes of the calibration cage, respectively (Fig. 1A). Similarly, flexion-extension angulations, internal-external rotations, and varus-valgus angulations relate to rotations around the x, y, and z axes, respectively. The two-dimensional (2D) translations under load, displacements in the coronal plane of each femur, were calculated as the vectorial sum ($\sqrt{x^2 + y^2}$) of mediolateral and proximodistal translations. The clinical and radiographic progress of each patient, documented by the consulting surgeon at each followup, also was reviewed.

Fig. 1A–B (A) A photograph of the DLRSA setup shows the calibration cage in the vertical position behind the patient and two radiographic tubes angled across the lower limb. The inset shows the x, y, and z axes of the calibration cage, which are used to measure translations in the mediolateral, proximodistal, and anteroposterior

planes, respectively. (B) A photograph of the DLRSA setup shows the digital scale positioned beneath the injured limb. The patient and digital scale are positioned on the patient lifter, enabling the patient's height to be altered easily.

Results

Taking RSA radiographs while simultaneously applying axial load was feasible in a clinical setting. There were no complications of the surgery relating to the insertion of the RSA beads (Fig. 2). The beads were sufficiently visible in each DLRSA examination. Adequate spatial orientation was achieved similarly, with a mean condition number of 84 (range, 38–142). All six patients were able to follow DLRSA instructions without difficulty with the exception of Patient E at the first (6-week) visit when the 20-kg minimum load was too uncomfortable to apply. There were no difficulties during subsequent visits. Only two pairs of RSA radiographs were unable to be analyzed, both in the final week of assessment with the midrange load of 40 kg. In the first case, one of the files was accidentally permanently deleted, and in the other case, the exposure was insufficient to enable clear registration of the beads.

We used the DLRSA technique to directly measure interfragmentary displacements under differential loads during healing (Table 2). During each DLRSA examination at every time for each patient, the 2D displacement increased as the load applied was increased (Fig. 3). The 2D translations recorded for three patients (Patients D, E,

and F) progressively decreased at each time between the 6- and 26-week examinations and the 2D translations of two patients (Patients B and C) also decreased at the 26-week examination. However, in contrast, the 2D translations of Patient A increased with time. For Patients C, D, E, and F, the position of the distal fracture fragment on postload radiographs had rotated by less than 0.2° from the original position in the preload radiographs. This indicates no permanent displacements occurred as a direct result of the investigation. Clinical assessment of these patients, including review of conventional radiographs, showed variable progression toward union during the 6 months for five patients (Patients B, C, D, E, and F). Patient A, however, did not progress and subsequently required additional surgery for nonunion.

Discussion

The inability to accurately and objectively assess the mechanical properties of healing fractures *in vivo* influences clinical fracture management and research. The aims of this study were to determine the feasibility of taking RSA radiographs while simultaneously applying axial load in a clinical setting and to apply this technique to monitor interfragmentary displacements under differential loads during healing.

Clinical limitations of DLRSA examinations are that they are time-consuming, require bead insertion, and are reliant on patient cooperation. The DLRSA method requires specialized equipment and involvement of experienced RSA users, both of which add considerable cost to clinical studies. Substantial cost (approximately \$60,000) is incurred initially to purchase the software, calibration cage, and bead insertion gun. A patient lifter platform also was purchased for approximately \$2000 specifically to enable DLRSA studies. Ongoing costs include purchasing tantalum beads at approximately \$4 per bead, and salaries for qualified radiographers and appropriate science graduate personnel who have been trained to analyze RSA radiographs and interpret results. We estimate the salary costs involved for one DLRSA examination to be \$30. Interfragmentary displacements measured using DLRSA depend on adequate spatial spread of beads in each of the fracture fragments and the condition number should be monitored for each patient. Consistent positioning of the markers in the bone fragments is important so similar fractures treated by different fixation techniques can be compared. Another limitation of the DLRSA method described in this article is it only assesses the stiffness of the fracture under a predominantly axial load. This method has been developed because the standard patient management clinical protocol emphasizes such a loading pattern. During

Fig. 2 A postoperative anteroposterior radiograph for Patient F shows the tantalum markers visible above and below the fracture line.

Table 2. Translations and rotations of the distal femoral condyle

Patient	Weeks postoperatively	Load (kg)	Translations (mm)			Rotations (degrees)		
			Medial (+) Lateral (−)	Proximal (+) Distal (−)	Anterior (+) Posterior (−)	Flexion (+) Extension (−)	Internal (+) External (−)	Varus (+) Valgus (−)
A	6	10	0.42	0.42	0.16	−0.2	0.3	0.8
		Postload	0.01	0.01	−0.10	−0.8	−0.3	0.2
		20	1.35	0.63	−0.25	0.0	2.1	1.1
	12	30	3.59	2.01	0.51	−0.9	2.2	4.7
		Postload	−0.16	−0.11	0.18	0.2	0.1	−0.3
		20	0.35	0.36	−0.27	0.3	0.5	0.4
	18	30	2.84	1.79	0.51	−0.4	1.0	4.1
		Postload	−0.18	−0.17	−0.25	0.2	−0.5	−0.2
		20	2.24	1.28	0.99	−0.1	1.3	3.7
	26	30	3.95	2.22	1.15	−0.2	1.7	6.6
		Postload	0.32	0.05	0.26	0.4	0.1	0.8
B	6	20	−0.27	0.96	0.71	−0.3	1.0	0.7
		Postload	0.43	−0.26	−0.20	0.4	−0.3	−0.2
		20	0.06	−0.99	0.43	−0.7	0.4	−1.6
	12	40	−0.09	−1.44	−1.20	0.9	0.6	−2.0
		Postload	−0.51	−1.61	−0.81	1.1	−0.1	−2.0
		20	0.31	0.26	−0.06	−0.3	0.5	−0.2
	18	40	0.75	1.81	−0.21	−0.9	0.9	−1.4
		Postload	−0.01	0.23	−0.12	−0.5	0.4	−0.1
		20	0.15	0.08	−0.67	0.3	0.6	−0.3
	26	40	0.15	0.73	−1.05	−0.1	1.2	0.6
		Postload	−0.14	0.01	−0.16	0.1	0.5	−0.1
C	6	20	−0.01	0.23	0.32	−0.7	0.4	0.4
		30	0.05	0.38	0.35	−0.9	0.7	0.7
		Postload	−0.17	−0.10	0.34	−0.4	0.4	−0.2
	12	20	0.18	0.26	0.15	−0.2	−0.1	0.6
		40	0.36	0.75	0.07	−0.2	0.3	1.3
		Postload	0.15	0.05	0.00	0.1	0.0	0.3
	18	20	0.06	0.20	0.20	−0.8	0.4	0.1
		40	0.35	0.53	0.23	−1.3	−0.3	0.7
		50	0.34	0.70	0.38	−2.3	0.4	−0.6
		Postload	0.03	0.02	−0.05	−0.1	−0.2	−0.1
	26	20	0.05	0.11	0.00	0.0	0.1	−0.1
		50	0.13	0.45	0.28	−0.8	0.2	0.7
		Postload	−0.03	−0.06	−0.04	0.3	−0.5	−0.2
D	6	20	1.42	−0.20	−0.54	1.0	0.1	1.2
		40	2.15	−0.16	−0.49	0.5	0.0	1.7
		60	2.71	−0.20	−0.54	0.9	1.3	2.1
		Postload	−0.18	0.07	0.01	0.4	0.6	−0.4
	12	20	0.32	0.05	−0.42	0.3	−0.5	0.3
		40	0.66	−0.02	−0.40	0.4	−0.6	0.8
		60	1.06	0.13	−0.58	0.4	−0.9	1.3
		Postload	0.08	−0.08	−0.50	0.5	−0.3	0.1
	18	20	−0.02	−0.10	−0.62	0.4	−0.5	0.2
		40	0.13	−0.01	0.51	−1.4	−1.9	0.3
		60	0.34	−0.01	0.73	−1.6	−0.8	0.6
		Postload	0.13	0.05	−0.19	0.2	−0.1	0.1

Table 2. continued

Patient	Weeks postoperatively	Load (kg)	Translations (mm)			Rotations (degrees)		
			Medial (+) Lateral (−)	Proximal (+) Distal (−)	Anterior (+) Posterior (−)	Flexion (+) Extension (−)	Internal (+) External (−)	Varus (+) Valgus (−)
E	26	20	0.04	−0.01	0.60	−0.6	−0.8	0.0
		40	−0.07	0.03	0.14	−0.1	0.3	0.1
		60	0.27	0.01	0.54	−0.8	0.0	0.4
		Postload	0.12	−0.05	0.22	−0.3	−0.3	0.1
	12	20	1.53	0.35	−1.76	2.3	4.3	0.6
		Postload	0.06	−0.07	−0.57	0.9	−0.2	−0.2
	18	20	−0.09	0.11	0.83	−0.6	−0.6	−0.1
		40	0.17	0.08	−0.01	−0.2	0.6	0.1
		Postload	−0.21	0.06	−0.03	−0.1	−0.8	−0.2
	26	20	−0.03	−0.04	0.01	1.0	0.3	−0.1
		40	0.11	0.00	0.07	1.5	0.2	0.2
		60	0.23	−0.05	−0.32	0.5	1.0	−0.2
		Postload	0.03	−0.02	−0.10	0.3	0.1	0.0
F	6	20	0.66	1.64	−0.34	0.7	1.8	2.0
		Postload	−0.24	−0.28	−0.01	1.1	0.0	0.4
	12	20	0.98	1.03	0.44	−0.9	−0.2	1.1
		40	2.07	1.27	0.39	−2.7	0.2	2.2
		Postload	−0.01	0.51	−0.18	−0.4	−0.1	−0.5
	18	20	0.19	0.08	0.11	1.3	−0.8	−0.5
		40	0.68	0.39	0.65	−0.4	0.1	0.4
		60	−1.17	0.72	0.74	−2.1	0.2	1.5
		Postload	0.02	0.11	0.11	0.2	−0.1	0.0
	26	20	0.01	0.06	0.18	0.6	−0.7	−0.5
		60	0.15	0.14	0.17	0.2	−0.3	−0.2
		Postload	−0.07	0.00	0.23	−0.5	0.2	0.1

this loading, however, the probability exists that a proportion of this axial load is redirected into angular and rotational vectors. The feasibility of using other load patterns with DLRSA, such as torsion or bending, has yet to be determined. Muscle activity during loading also was not investigated as part of this study, but the axial loading technique was designed to minimize this effect. Future DLRSA studies are planned using different loading regimes, including loading associated with muscle activity. Currently, loads are applied in 20-kg increments, but it is predicted, with additional data, a smaller number of load increments will be required to yield meaningful data. These reductions would further reduce radiation exposure, examination time, and costs.

The DLRSA method developed during this study was feasible in a clinical setting and includes techniques for load application and measurement, patient positioning, and radiographic equipment setup. It allowed interfragmentary displacements to be measured directly under load in lower limb fractures treated with internal fixation devices. The magnitude of the translations and rotations recorded were

well above those reported for in vitro precision of RSA when used to investigate distal femur fractures [16]. The accuracy and precision of DLRSA results will be different for each fracture type and therefore additional dedicated validation studies are required.

We successfully used DLRSA examinations for distal femur fractures. The current load versus displacement plots are not consistently linear except in the latter stages of cases that progressed to union. In the early stages of healing, in which there is marked comminution or a large fracture gap, the initial stiffness recorded is essentially that of the fixation device with or without further influences from forces on the fracture fragments arising from attached muscles. As healing progresses, there is an increasing influence of the callus mechanical properties on the overall stiffness of the composite construct. At the time of healing, the measured stiffness is likely to be almost entirely the result of that of the fracture callus, but only if it is measured in planes in which the stiffness of the healed bone exceeds that of the fixation device. With the lateral plate used in this study, the coronal plane is therefore the main

Fig. 3A–F The line graphs show 2D translations under differential load at 6, 12, 18, and 26 weeks for (A) Patient A, (B) Patient B, (C) Patient C, (D) Patient D, (E) Patient E, and (F) Patient F. The x axis

of each graph represents the amount of 2D translations recorded (mm) and the y axis represents the amount of load applied (kg).

plane of interest [11, 16]. Additional studies to assess and model the specific contribution of each component in this composite construct will help optimize the analysis of the findings.

Although having great application in clinical fracture research and investigating interfragmentary displacement on an individual patient basis, DLRSA is unlikely to find a place in everyday clinical practice. It is not yet possible to define an end point to fracture healing based on mechanical criteria; however, the data do provide objective and quantifiable mechanical properties at a given time that can be used to monitor progression. Only limited comparisons

can be made between the findings of this study and others that measured mechanical properties during healing using techniques reliant on external fixation devices. Although measurements of stiffness can be made from calculating displacements from strain detected around the different axes of an external fixator, the mechanical constraints of the fixation are clearly different from those of an internal fixation device, as are the loads applied. The end point stiffness value of 15 Nm/degree defined for external fixation cannot be directly extrapolated to this technique, and at this stage, there are insufficient data to allow correlations to be developed.

Because of the small number of patients in this feasibility study, we did not attempt to correlate the progression of DLRSA stiffness measurements with clinical assessment. However, the only patient to be assessed clinically as having a nonunion and require revision surgery was the same patient who did not show an increase in DLRSA stiffness results with time.

The data from future DLRSA studies may lead to better understanding of the mechanics of the fracture healing process and the ability to better rationalize management of patients with fractures. The ability to study the effect of fixation stability on fracture healing in patients treated with bridging locking plates is an area that would greatly benefit from this methodology. This would allow us to study the effect of construct configuration and application and how these might be optimized with respect to fixation stability. It should also enhance our ability to objectively study new biologic treatments aimed at improving fracture healing. With further development, it is predicted DLRSA examinations may become as useful in trauma management research as RSA has become in arthroplasty.

DLRSA is a new method that monitors fracture stiffness in vivo by directly measuring interfragmentary displacements under varying loads during healing. It has the potential to be used as a new clinical research method to measure healing fracture stiffness and to allow objective comparisons between different treatment modalities.

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