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Biomarkers affected by impact velocity and maximum strain of cartilage during injury

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ABSTRACT

Osteoarthritis is one of the most common, debilitating, musculoskeletal diseases; 12% associated with traumatic injury resulting in post-traumatic osteoarthritis (PTOA). Our objective was to develop a single impact model with cartilage "injury level" defined in terms of controlled combinations of strain rate to a maximum strain (both independent of cartilage load resistance) to study their sensitivity to articular cartilage cell viability and potential PTOA biomarkers. A servo-hydraulic test machine was used to measure canine humeral head cartilage explant thickness under repeatable pressure, then subject it (except sham and controls) to a single impact having controlled constant velocity $V=1$ or 100 mm/s (strain rate 1.82 or 182/s) to maximum strain $\varepsilon=10\%$, 30%, or 50%. Thereafter, explants were cultured in media for twelve days, with media changed at day 1, 2, 3, 6, 9, 12. Explant thickness was measured at day 0 (pre-injury), 6 and 12 (post-injury). Cell viability, and tissue collagen and glycosaminoglycan (GAG) were analyzed immediately post-injury and day 12. Culture media were tested for biomarkers: GAG, collagen II, chondroitin sulfate-846, nitric oxide, and prostaglandin E_2 (PGE_2). Detrimental effects on cell viability, and release of GAG and PGE_2 to the media were primarily strain-dependent, (PGE_2 being more prolonged and sensitive at lower strains). The cartilage injury model appears to be useful (possibly superior) for investigating the relationship between impact severity of injury and the onset of PTOA, specifically for discovery of biomarkers to evaluate the risk of developing clinical PTOA, and to compare effective treatments for arthritis prevention.

1. Introduction

Osteoarthritis (OA) is a painful and debilitating whole joint disease involving cartilage degradation, sclerosis of subchondral bone, and inflamed synovial tissue anticipated to affect 59 million Americans by 2020 (Lawrence et al., 1998). Out of 46 million Americans currently diagnosed with OA, approximately 12% are associated with traumatic injuries resulting in annual costs over 3 billion dollars (Brown et al., 2006). Although the exact etiology and pathogenesis of OA is often unknown, acute joint trauma during sports injuries, vehicular accidents, or falls may initiate a common series of events culminating in post-traumatic osteoarthritis (PTOA) (Buckwalter and Brown, 2004). Pathologic responses reported for mechanically-injured cartilage include cell (chondrocyte) death (Jeffrey et al., 1995; Torzilli et al., 1999; Loening et al., 2000; Kurz et al., 2001; Milentijevic et al., 2003; Milentijevic and Torzilli, 2005; Huser and Davies, 2006; Torzilli et al., 2006), direct tissue disruption with loss of cartilage proteoglycan (DiMicco et al., 2004; Huser and Davies, 2006; Natoli et al., 2008; Borrelli et al., 2009) and collagen II (Mrosek et al., 2006; Borrelli et al., 2009), and increased release of prostaglandin E_2 (Jeffrey and Aspden, 2007; Joos et al., 2011) and nitric oxide (Loening et al., 2000; Green et al., 2006; Ewers et al., 2001). However, the severity of injury to cartilage, and the rate and magnitude of impact loading (trauma severity) to initiate this process, as well as the subsequent pathologic changes in cartilage's functional material properties and corresponding relationship with its biochemical changes are not fully understood.

A variety of models have been used to deliver and investigate the effect of rate and magnitude of impact load (Table 1). Ideally, a quantifiable and repeatable severity of injury model's controlled impact parameters would be independent of the cartilage's thickness and biomechanical resistance and health characteristics. This is impossible when using energy of the impacting object, stress rate, or maximum stress as the controlled parameters, since they

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Table 1
Summary of investigations into effect of impact magnitude and/or rate on tissue parameters and constituents released to culture media.

Author	Impact/ loading device[a]	Explant			Reported impact			Impact equivalent[e]	
		Species[b]	Constraint[c]	Cartilage pre-impact thickness T_i (mm)[d]	Magnitude used to stop loading	Rate or duration	Max axial strain	Strain rate (1/s)	Velocity (mm/s)
Strain rate controlled impact									
Waters	SH	C_h	RC_w	0.55	10, 30, 50% strain	1, 100 mm/s	0.1–0.5	1.8, 182	1, 100
Morel and Quinn (2004)	ED	B_h	RU/SB	NR	3.5, 7, 14 (MPa)	$7 \times 10^{-5,-4,-3,-2,-1}$ (strain/s)	0.82–0.54	<0.7	<1.1
10 days									
Quinn et al. (2001)	ED	B_s	RU	NR	3.5, 7, 14 (MPa)	3×10^{-5} (strain/s)	0.83–0.93	3×10^{-5}	$4.5 \times 10^{-5}_{\bar{Ti}=1.5}$
						0.3, 0.5, 0.7 (strain/s)	0.43–0.68	0.3, 0.5, 0.7	$0.45–1.05_{Ti=1.5}$
Stress rate controlled impact									
Ewers et al. (2001)	SH	B_m	RU	NR	40 (MPa)	40 (MPa/s)	0.476	0.44	$0.7_{Ti=1.5}$
					40 (MPa)	930 (MPa/s)	0.409	8.38	$12.6_{Ti=1.5}$
Milentijevic et al. (2003)	SP	B_k	$RC_w - Por_{wb}$	1.46	10–60 (MPa)	350 (MPa/s)	0.02–0.23	<1.2	<1.5
Milentijevic et al. (2005)	SP	B_k	$RC_w - Por_{wb}$	1.26	10, 20, 30, 40 (MPa)	25, 50, 130, 1000 (MPa/s)	0.23–0.11	<1.2	<1.5
Milentijevic et al. (2005)	SP	R_{fc}	RCc, Viv	0.7	15–50 (MPa) 35 (MPa)	420 (MPa/s) 420	–	–	–
D'Lima et al. (2001)	SH	B_k H_{ftp}	RU	1–1.8	7, 14, 23 (MPa)	100 min to final stress	0.40, 0.67, 0.72–0.83	<0.09	<0.16
Energy of impacting object controlled									
Jeffrey et al. (1995)	DT	B_m	RU	NR	12 mass-drop heights creating 0.049–1.96 (J)	1600 to 2300 initial (strain/s) (reported for 3 of 12 mass-drop)	0.8–0.87 (3 example mass-drop)	–	$630_{Vi}–3130_{Vi}$
Jeffrey et al. (2006)	Scr	H_f	RU	NR	Max strain = average from drop tower	40 (mm/s)	NR	–	40
	DT	H_f	RU	NR	0.12 (J)	1.5 ms to peak load	NR	–	693_{Vi}
Bush et al. (2005)	DT	B_m	RU	NR	0.049, 0.098, 0.196 (J)	–	–	–	$990–1400_{Vi}$
Duda et al. (2001)	DT	P_p	RC_c	NR	0.06, 0.1, 0.2 (J) Spheric Indentor	–	–	–	$1095, 1414, 2000_{Vi}$
Haut et al. (1995)	DT	R_{pf}	Viv	NR	0.9, 4.2, 6.3 (J)				$2046, 2513, 3078_{Vi}$
Huser and Davies (2006)	DT	E_i	RU	NR	0.123, 0.245, 0.490 (J)	–	–	–	$701, 1008, 1400_{Vi}$
Flachsmann et al. (2001)	DP, ST	B_p	RC_c/SB	1.5	Strain taken at 4,10,15,20,25 (MPa) 15 (MPa)	$V_{\text{"constant"}} = 2000$ (mm/s)	<0.25 0.75	1333 "nominal"	$?_{Vi}$
Ewers et al. (2002)	SH	R_{pf}	Viv	NR	590 (N)	50 ms to peak load	–	–	–
	DT	R_{pf}	Viv	NR	630 (N)	5 ms to peak load	–	–	–
Static (constant) load – creep test									
Torzilli et al. (2006)	Cr	B_k adult calve	$RC_w - Por_{lp}$	2	0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7 (strain) in less than 1 s	Static stress adjusted to produce similar time to reach strain level	–	<1.4 assuming 0.5–1 s to reach stress level	–