MECHANICAL CHARACTERIZATION OF INTERNAL LAYER FAILURE IN THE HUMAN CAROTID ARTERY

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ABSTRACT

Blunt carotid artery injuries are commonly characterized by intimal failures leading to vessel dissection, resulting in cerebral infarction and ischemic stroke. These injuries typically occur in motor vehicle collisions and, although the incidence is low, are associated with high morbidity and mortality rates. Previous studies of arterial failure mechanics did not quantify intimal failure. The present study quantified intimal failure mechanics relative to catastrophic vessel failure in human and porcine arteries. Under mechanical distraction, human internal and common carotid arteries demonstrated similar behavior, with only ultimate stress being significantly different ($p<0.05$). Porcine aortas sustained significantly greater stress and strain at initial intimal failure, strain at ultimate failure, and intimal-to-ultimate stress and strain ratios. Human carotid arteries were obtained from cadavers of advanced age that were frozen prior to excision. Because these factors may alter soft-tissue mechanical response, young, fresh porcine aortas are likely a better model of blunt carotid artery injury. This study provides a mechanical basis for clinical findings of intimal failure in blunt carotid artery injury.

Key Words: biomechanics, side impacts, rear impacts, neck, injuries, carotid artery

CAROTID ARTERIES ARE THE PRIMARY means of blood supply to the organs of the head-neck complex. These arteries consist of heterogeneous anatomy with three primary layers: intima, media, and adventitia in the internal, middle, and outer vessel regions, respectively. Disruption of a single layer can cascade into catastrophic vessel failure over time. Injuries to the carotid artery can result from blunt or penetrating trauma. Blunt carotid artery trauma has been clinically associated with high rates of morbidity and mortality. The most commonly associated mechanisms of blunt injury include motor vehicle collisions, sporting accidents, and blunt strike to the neck region (e.g., assault, automotive seatbelt) (Biffl *et al.* 1999; Crissey and Bernstein 1974; Zelenock *et al.* 1982). In particular, these mechanisms may stretch the vessel beyond its physiologic limit leading to failure of internal vessel layers (e.g., intima), while external layers remain intact (Cogbill *et al.* 1994; Crissey and Bernstein 1974; Fabian *et al.* 1996; Krajewski and Hertzer 1980; Sullivan *et al.* 1973). It was reported that 62% of blunt carotid artery patients in which the pathology was definitely known sustained intimal tear (Yamada *et al.* 1967). Because outer layers remain intact, the vessel remains acutely capable of maintaining normal physiologic function, which often results in delayed symptomology of several hours to days (Alimi *et al.* 1998; Cogbill *et al.* 1994; Crissey and Bernstein 1974; Fabian *et al.* 1996; Krajewski and Hertzer 1980).

Complications associated with intimal failure in blunt carotid artery trauma include ischemic stroke and cerebral infarction resulting primarily from progressive dissection and eventually vessel occlusion (Fabian *et al.* 1996; Mokri *et al.* 1988; Pretre *et al.* 1994). Additionally, an embolism may develop due to platelet aggregation on the denuded intima. These mechanisms are associated with delayed symptomology as neither results in immediate vessel occlusion. In a six-year multi-center study, 29% of patients with carotid artery injury developed neurologic deficit greater than 12 hours after initial examination (Cogbill *et al.* 1994). In that study, 72% of injuries were attributed to motor vehicle collisions. Another study investigating blunt carotid artery injuries over a ten-year period reported that 50% of these patients demonstrated neurologic deficit not consistent with computed tomography (CT) findings at initial examination (Carrillo *et al.* 1999). That study attributed 85% of blunt carotid artery

injuries to motor vehicle collision. Although incidence estimates are low, blunt carotid artery injuries result in devastating morbidity (20-75%) and mortality (5-40%) rates (Biffl *et al.* 1998; Fabian *et al.* 1996; Krajewski and Hertzer 1980; Miller *et al.* 2002; Parikh *et al.* 1997; Pretre *et al.* 1994). Initial incidence estimates for blunt carotid artery injury were 0.08 to 0.17% of all patients with blunt injuries (Davis *et al.* 1990; Ramadan *et al.* 1995). However, a more recent study estimated that the actual incidence is closer to 1.2% due to a high percentage of these injuries being missed at initial examination because of delayed symptomology or more immediately serious injuries (Biffl *et al.* 2002). Injuries most commonly associated with blunt carotid artery trauma include craniofacial trauma, cervical spine fracture, and closed head trauma (Davis *et al.* 1990; Fabian *et al.* 1996; Parikh *et al.* 1997). However, the likelihood of intimal layer failure prior to catastrophic vessel failure, the mechanism responsible for delayed symptomology, remains unexplored.

Failure mechanics of blunt carotid artery injury are poorly understood. Previous studies investigated catastrophic failure mechanics of human blood vessels such as cortical arteries and descending aortas (Lee and Haut 1989; Mohan and Melvin 1982; Monson *et al.* 2003). In addition, failure mechanics of rat and mouse carotid arteries have been studied (Cohuet *et al.* 2001; Lacolley *et al.* 2001). These studies quantified ultimate vessel failure characteristics in terms of stiffness, stress, and strain, but failed to identify mechanics of intimal layer failure. By increasing intraluminal static pressure in excised rat carotid arteries, one study demonstrated incomplete, longitudinal or transverse ruptures of internal vessel layers (Cohuet *et al.* 2001). These failures involved the internal elastic lamina and, in some specimens, a portion of the media. However, the loading technique used in that study subjected vessels to transverse strain through internal pressurization and not longitudinal strain. In addition, that study did not quantify mechanical properties associated with internal layer failure. To date, the mechanical relationship between failure of the intimal layer and catastrophic vessel failure has not been experimentally defined.

The purpose of the present investigation was to determine whether intimal layer failure occurs prior to ultimate (catastrophic) vessel failure. Mechanics of intimal layer failure in terms of stress and strain were quantified relative to ultimate vessel failure using human internal and common carotid arteries and porcine descending thoracic aortas. Histology was used to characterize pathology of intimal layer failure. This study determined the suitability of porcine descending aortas as a model of blunt carotid artery injuries.

METHODS

Seven internal and 15 common carotid arteries were harvested from human cadaver subjects that were frozen prior to autopsy. Cadaver specimens had a mean age of 62 years, and were used in a separate testing protocol. In addition, 18 descending thoracic aortas were harvested from fresh porcine subjects sacrificed at approximately six months of age secondary to a separate experimental protocol. Previous testing of human and porcine subjects did not affect mechanical properties of the carotid or aortic vasculature. Initial length of the vessels was measured prior to (*in situ*) and immediately after (*in vitro*) excision. The *in vitro* length relative to the *in situ* length determined the retraction ratio. Loose adventitial and connective tissue was removed from the vessels, which were then placed in lactated Ringer's solution and refrigerated at +4 deg Celsius for less than 24 hours prior to mechanical testing.

SPECIMEN PREPARATION: Arterial vessels were prepared for mechanical testing by opening the vessels at the mid-diameter level to expose the internal side. For porcine specimens, the incision was made along the dorsal side, following the line of arterial branches. With the exception of the external/internal carotid branch, no arterial branches exist for the common or internal carotid arteries inferior to the skull. Vessels were laid flat and I-shaped mechanical test specimens were cut using a custom-designed die to the dimensions presented in Fig. 1. The greatest test specimen width was approximately 50% of the vessel circumference. The purpose of the I-shaped test configuration was to concentrate failure in the middle of the specimen and avoid fixation failures. Specimens were periodically soaked in Ringer's solution to prevent dehydration and maintain elastic properties.

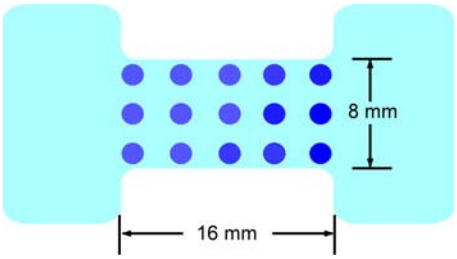

Fig. 1 – Arterial test specimen.

MECHANICAL TESTING: The mechanical testing protocol for human carotid artery specimens was published previously and will be summarized here (Stemper *et al.* in press). Mechanical tensile loads were applied to the test specimens using the loading apparatus illustrated in Fig. 2. Specimens were fixed to the loading apparatus at the superior and inferior ends using custom-designed fixation devices. Thirty-gauge wire mesh was used as an interface between metal fixation surfaces and the specimen to prevent slippage and fixation failures. The inferior end of the specimen was attached to the test frame through a load cell. The superior end of the specimen was attached to the piston of an electrohydraulic testing device (MTS Systems Corp., Eden Prairie, MN, USA). A load cell was also attached in series between the piston and the superior fixation device. Vertical displacement of the piston was measured using a linear variable differential transducer (LVDT). Piston displacement corresponded to global stretch of the vessel, as the inferior end was fixed. High-resolution digital video cameras were oriented perpendicular to the intimal plane and at approximately 30 deg. from the adventitial plane (Redlake Inc., San Diego, CA, USA). The intimal camera was oriented to identify internal layer failure prior to catastrophic vessel failure. The adventitial camera was used to confirm vessel integrity prior to catastrophic vessel failure. Due to high-powered lights on the specimen from the intimal side, the adventitial camera was not positioned directly perpendicular to the adventitial plane.

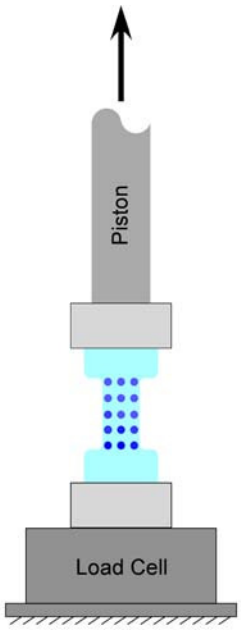

Fig. 2 - Testing apparatus.

Prior to testing, specimens were oriented to the *in vitro* length, corresponding to zero stress. Digital calipers were used to measure specimen width and wall thickness. The vessel was preconditioned for five cycles at 1.0 mm/sec to approximately the *in situ* length to restore mechanical properties to *in vivo* conditions by stabilizing the tissue and reducing hysteresis (Bergel 1961). Specimens were quasi-statically loaded in tension at 1.0 mm/sec until catastrophic vessel failure. The event was imaged from intimal and adventitial sides at 125 Hz. Mechanical data from the load cells and LVDT were gathered at 1,000 Hz and filtered using a 10 Hz low-pass filter. Loading data and digital videography were synchronized using a common trigger.

DATA REDUCTION: Using initial specimen length and cross-sectional area in conjunction with axial loading and LVDT temporal data, engineering stress and longitudinal strain information were extracted. Global strain was defined as displacement of the LVDT divided by the initial vertical distance between inferior and superior fixation devices. Internal layer failure and catastrophic vessel failure were identified using videography and correlated with stress and strain data. Internal layer failure was defined as sub-catastrophic failure of the vessel, wherein only a portion of the vessel wall failed. Catastrophic failure was defined as complete transection of the vessel wall. In addition, ratios of stress and strain at intimal failure relative to ultimate vessel failure were calculated. Stress and strain values at intimal and ultimate failures, as well as ratios of intimal to ultimate failure were compared using single-factor unpaired t-tests, with significance level of α=0.05. Porcine descending aorta properties were also compared to human carotid artery mechanical properties using unpaired t-tests.

RESULTS

Forty vessels (22 human, 18 porcine) were excised and mechanically distracted until catastrophic vessel failure. After excision, human carotid arteries retracted to 91±3% of their original *in situ* length whereas porcine aortas retracted to 78±5% of their *in situ* length. With the exception of one human and three porcine arteries, all specimens demonstrated intimal layer failure prior to catastrophic vessel failure. In most cases, multiple intimal failures were evident. Intimal failures generally occurred in the 'web' of the I-shaped test specimens, with only one failure occurring at the intersection of the 'flange' and the 'web'. Orientation of intimal failures was primarily transverse (perpendicular to the direction of loading). Intimal failure was defined using high-resolution videography. The adventitial camera confirmed integrity of the adventitial side until catastrophic vessel failure. Representative stress versus strain plots are provided in Fig. 3, with occurrence of initial intimal failure noted.

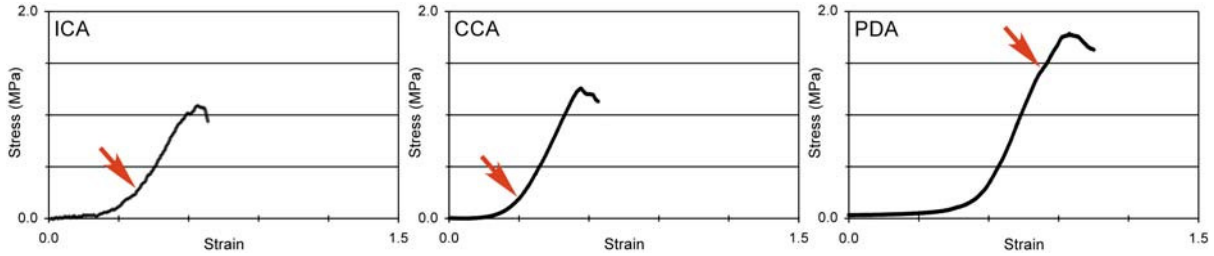

Fig. 3 – Representative stress-strain plots for internal (ICA) and common (CCA) carotid arteries and porcine descending aortas (PDA). Occurrence of initial intimal failure is noted.

Mechanical parameters (stress and strain) associated with initial intimal failure, ultimate failure, and the ratio of intimal to ultimate failure for internal and common carotid artery specimens are presented in Fig. 4. Time of initial intimal failure, obtained from digital videography, was correlated to stress versus strain plots. Ultimate failure was defined as the peak of the stress versus strain plot and corresponded approximately with the time of catastrophic vessel failure as determined using videography. Mechanical properties of internal and common carotid artery specimens were not significantly different for all measures, with the exception of stress at ultimate failure (Fig. 4). Ultimate failure occurred at 1.5±0.3 MPa for common and 1.0±0.3 MPa for internal carotid artery specimens ($p<0.01$). Initial intimal failure occurred at approximately 44% stress and 60% strain to ultimate vessel failure in human carotid arteries.

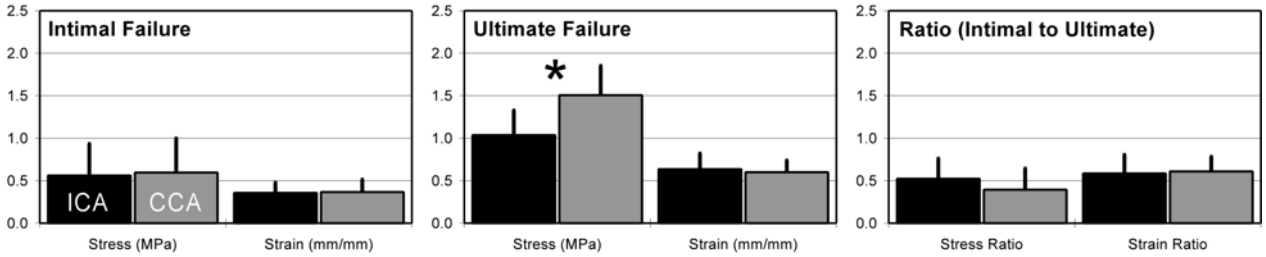

Fig. 4 – Failure mechanics from internal (ICA) and common (CCA) carotid artery specimens.

Porcine descending thoracic aorta specimens were also tested under the current protocol. Young, fresh porcine aortas had similar dimensions to human carotid arteries. In particular, outer vessel diameter was 8.5±1.5 mm in porcine and 8.9±2.0 mm in human specimens. Wall thickness was 1.2±0.4 mm in porcine and 1.1±0.4 mm in human vessels. Because mechanical properties of human internal and common carotid artery specimens were primarily not significantly different, internal and common carotid specimens were grouped for comparison to porcine aorta specimens. Porcine specimens sustained significantly greater stress and strain to initial intimal failure ($p<0.001$) than human specimens (Fig. 5). In addition, strain to ultimate failure was significantly greater ($p<0.01$) in porcine than in human specimens. Although stress to ultimate failure was greater in porcine specimens (1.6±0.7 MPa in porcine compared to 1.3±0.4 MPa in human specimens), this difference only approached statistical significance ($p=0.14$). Initial intimal failure occurred significantly later in

porcine than in human specimens; 78.5±17.7% of the stress and 85.0±9.0% of the strain to ultimate failure in porcine compared to 43.7±24.7% and 60.1±18.3%, respectively, in human specimens.

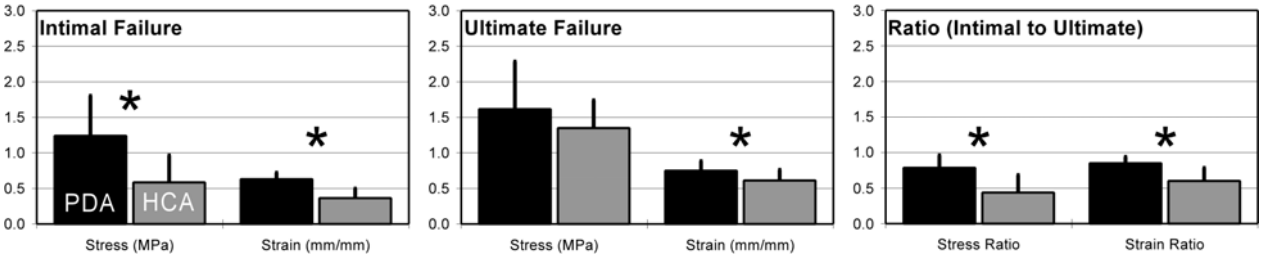

Fig. 5 – Failure mechanics from human carotid (HCA) and porcine aorta (PDA) arterial specimens.

Intimal failure pathology was similar between porcine and human specimens. Separate from the current protocol, a single porcine aorta specimen and a single human carotid specimen were distracted until initial intimal failure, then removed from the testing device and examined using histology. A representative histology slice from each specimen is demonstrated in Fig. 6. Intimal failure in both arteries transected the intimal layer and involved a small portion of the medial layer. The rest of the medial layer and entire adventitial layer were unaffected by intimal tear. Depth of intimal failure was approximately equal in both specimens.

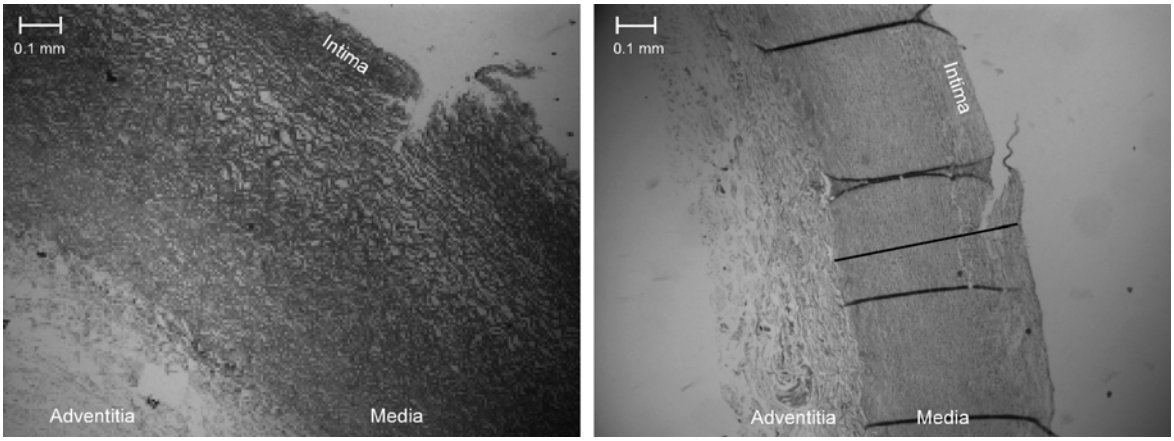

Fig. 6 – Subcatastrophic intimal failure of porcine (left) and human (right) specimens.

DISCUSSION

The present study subjected aged human internal and common carotid arteries as well as young porcine descending thoracic aortas to distraction magnitudes sufficient to result in catastrophic vessel failure. In a majority of arterial specimens (36/40 specimens), the intimal layer failed first, leaving medial and adventitial layers primarily intact until catastrophic vessel failure. This was confirmed using high resolution videography. Analysis of mechanical responses demonstrated no significant differences in stress or strain at initial intimal failure between common and internal carotid artery specimens. Stress at ultimate failure was significantly greater in common carotid specimens, although no differences were evident in strain to ultimate failure. Soft tissue failure can be considered a strain-mediated phenomenon because strain to failure remains approximately constant over a wide range of loading rates (Lee and Haut 1989; Lee and Haut 1992; McElhaney 1966; Mohan and Melvin 1982; Monson *et al.* 2003; Yoganandan *et al.* 1989). Therefore, all human carotid specimens were grouped for comparison to porcine descending thoracic aorta specimens. Human and porcine specimens were similar in geometry and histology. Young, fresh porcine specimens demonstrated significantly greater stress and strain to initial intimal failure, as well as strain to ultimate failure. In particular, and most relevant to the present study, initial intimal failure in porcine specimens occurred significantly later relative to catastrophic vessel failure (85%) than human specimens (60%). Present findings provide a mechanical basis for the clinical hypothesis that the intimal layer fails prior to catastrophic vessel

failure in blunt carotid artery injuries, leading to delayed symptomologies secondary to carotid artery occlusion.

Blunt carotid artery injuries most often occur in younger patients in the third and fourth decades (Biffl *et al.* 1998; Cogbill *et al.* 1994; Fabian *et al.* 1996; Miller *et al.* 2002; Parikh *et al.* 1997; Pretre *et al.* 1994; Sinson *et al.* 2003). However, human carotid arteries used in the present study were obtained from cadaver specimens of advanced age that were frozen prior to excision. In contrast, porcine aorta specimens were obtained from fresh, unfrozen animals aged approximately six months, and tested within 24 hours of sacrifice. Porcine aortas were a geometrically accurate model of human carotid arteries, with approximately equal outer diameter and wall thickness. In addition, histology demonstrated that porcine aortas sustained similar intimal layer pathology to human carotid arteries. For these reasons, it was determined that porcine aorta specimens were a better experimental model for *in vivo* blunt carotid artery injury. Mechanical differences existed between the two groups in stress and strain responses at intimal and ultimate failure. In particular, porcine specimens demonstrated greater stress and strain at initial intimal and ultimate failure, and greater intimal to ultimate failure ratios. These findings are consistent with previous studies investigating the effect of age on mechanical properties of arterial tissue, wherein increased stiffness in older human specimens (compared to younger porcine specimens) was attributed to a loss of elasticity (Carmines *et al.* 1991). This may explain early failure of the intimal layer relative to ultimate failure in human specimens in the present study, wherein younger porcine specimens demonstrated intimal failure much closer to ultimate failure magnitudes. Other studies support the finding of decreased elasticity with age (Mohan and Melvin 1982; van Andel *et al.* 2003). In particular, van Andel et al. (2003) demonstrated that younger specimens were 'approximately three times more elastic' than older specimens. Freezing of human specimens may also affect inherent mechanical properties. However, literature is inconclusive on this point. For example, porcine aorta specimens pressurized above the physiologic limit demonstrated only slight differences in characteristic mechanical response (Carmines *et al.* 1991). Other soft tissues, such as medial collateral ligaments, cervical musculature, and cervical and lumbar spine segments, demonstrated similar behavior between fresh and frozen tissue (McElhaney *et al.* 1983; Panjabi *et al.* 1985; Smeathers and Joanes 1988; van Ee *et al.* 1998; Woo *et al.* 1986). In contrast, studies using tendons, ligaments, and spinal motion segments demonstrated decreased stiffness after tissues were frozen (Callaghan and McGill 1995; Smith *et al.* 1996; Turner *et al.* 1988). Therefore, the effect of freezing on mechanical response of soft tissues remains unclear. Investigation of this effect on failure mechanics in arterial specimens remains a future direction of this research.

Arterial specimens were tested under quasi-static loading conditions in the present protocol. Slower loading rates are ideal to define inherent soft tissue mechanical properties. However, injuries to the carotid artery typically result from dynamic soft-tissue loading conditions that may affect intimal and ultimate failure properties. Previous studies hypothesized considerably higher strain rates for the human thoracic aorta in automotive collisions (Kivity and Collins 1974). Strain rates are likely to be even higher for the head-neck complex under inertial loading. However, the effect of strain rate on arterial failure mechanics has not been clearly outlined in literature. Previous studies using cortical arteries and ferret carotid arteries demonstrated that strain rate had no significant effect on ultimate strain and stress (Lee and Haut 1992; Monson *et al.* 2003). Other studies using human descending aortas and parasagittal bridging veins reported significantly increased ultimate stress magnitudes and, in the case of bridging veins, a strong dependence of ultimate strain (Lowenhielm 1974; Mohan and Melvin 1982). Present results can be used as a first approximation to define mechanics of intimal failure in arterial specimens. Future research will focus on the effect of strain rate on subcatastrophic and catastrophic tissue failure.

A limitation of the present protocol was that failure properties of the intimal layer were only quantified under longitudinal loading. Due to orientation of vessel fibers, it is possible that transverse loading, due to pressurization, may result in a different mechanical response. However, previous studies demonstrated minimal differences between longitudinal and transverse mechanical properties under physiologic loading conditions (Mohan and Melvin 1982; Sauren *et al.* 1983). Pressurization of the vessel adds an initial pre-stress that may decrease failure mechanics. However, due to pulsatile

blood flow, the magnitude of pre-stress will exhibit temporal variation. Therefore, blunt carotid artery injury may depend not only on the magnitude of longitudinal tension, but also the time in the cardiac cycle at which maximum tension occurs. The relationship between intimal failure, longitudinal tension, and vessel pressurization remains a future focus of this research.

Orientation of intimal failures was primarily transverse, perpendicular to the direction of loading. The carotid artery intimal layer consists of an endothelium and subendothelial layer. While the endothelium is very thin, the subendothelial layer consists of elastic fibers and collagen fibrils. Subendothelial fibers, oriented predominantly in the longitudinal direction, were loaded in tension during the present protocol. Localized failures of individual fibers weakened adjacent fibers, cascading transversely in both directions from the initial failure. Therefore, intimal failures oriented in the transverse direction are likely attributed to the direction of loading and fiber orientation, rather than directionally dependent material property values.

Present results compare well with previous studies investigating quasi-static failure mechanics of human descending thoracic aorta specimens (Mohan and Melvin 1982). Using I-shaped, longitudinally oriented mechanical test specimens, the previous study reported ultimate true stress and longitudinal strain values of 1.5±0.9 MPa and 0.5±0.2 mm/mm, respectively. Results from the present study were 1.6±0.7 MPa and 0.7±0.1 mm/mm. This comparison demonstrates minimal differences in failure mechanics between fresh human and porcine arterial specimens. In addition, results from the previous study support our assertion that increased age significantly decreases failure mechanics. For example, aorta specimens obtained from human subjects younger than 60 years demonstrated significantly greater ($p<0.05$) stress and strain to failure in that study. These results support the present assertion that young porcine aortas may be a better model for blunt carotid artery injury without catastrophic vessel failure.

The present study demonstrated susceptibility of the intimal layer to localized failure prior to catastrophic vessel failure. These results provide a biomechanical basis for the clinical finding of delayed symptomology in blunt carotid artery injured patients. Because the injury involves the entire intimal layer, as demonstrated in Fig. 6, arterial sub-failure can lead to peeling away of this layer as blood dissects the vessel. Eventually the intimal 'flap' may be large enough to occlude the vessel, greatly limiting blood flow to the brain (Biffl *et al.* 1999). Another mechanism could be platelet aggregation in the intimal tear region, with or without subsequent embolus formation, leading to eventual vessel occlusion. These injury mechanisms would result in delayed symptomology as vessel occlusion does not develop instantaneously and the vessel remains acutely capable of normal function. Delayed symptomology is the primary reason for high morbidity and mortality associated with blunt carotid artery injury. Therefore, to reduce the incidence of long-term neurologic deficit or mortality due to blunt carotid artery injury, aggressive screening for these injuries should be undertaken at initial examination for patients presenting with associated injuries suggestive of significant carotid artery stretch. If the injury is identified early, anticoagulation or endovascular stenting techniques permit repair of dissection prior to neurological deterioration (Fanelli *et al.* 2004; Liu *et al.* 1999; Malek *et al.* 2000).

CONCLUSIONS

The present study quantified failure mechanics of the arterial intimal layer under longitudinal tension. To our knowledge, this is the first study to quantify intimal failure relative to catastrophic vessel failure. Human common and internal carotid arteries and porcine descending thoracic aortas were mechanically distracted until catastrophic failure. The intimal layer failed prior to ultimate vessel failure in 90% of arterial specimens. Intimal failure mechanics were not significantly different between internal and common carotid specimens, wherein initial intimal failure occurred at 36% strain and 0.59 MPa. However, intimal failure occurred significantly later in fresh, young porcine specimens (63% strain and 1.24 MPa). Due to limitations in specimen quality of human carotid arteries (i.e., advanced age and less than ideal storage methods), the porcine aorta is likely a better model for blunt carotid artery injury resulting in subcatastrophic arterial failure. Therefore, to reduce the incidence of long-term neurologic deficit or mortality due to blunt carotid artery injury, aggressive screening for

these injuries should be undertaken at initial examination for patients presenting with associated injuries suggestive of significant carotid artery stretch.

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