The Influence of Breast Reconstruction Choice on Functional Shoulder Biomechanics in Women Undergoing Mastectomy for Breast Cancer

by

Joshua Michael Leonardis

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Doctoral Committee:

Assistant Professor David B. Lipps, Co-Chair
Associate Professor Adeyiza O. Momoh, Co-Chair
Associate Professor Deanna H. Gates
Associate Professor Richard E. Hughes

Joshua M. Leonardis

jleo@umich.edu

ORCID iD: 0000-0002-4885-9186

Dedication

To my parents, Karen and Ed, who taught me to will it into existence.

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Preface

The chapters of this dissertation have been written as separate manuscripts for submission. There may be repetition between the chapters with regard to content. Chapter Two has been published in *Breast Cancer Research and Treatment*. Chapter Three has been accepted for publication in *Plastic and Reconstructive Surgery*. Chapter Four has been published in the *Journal of Orthopaedic Research*.

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Abstract

A majority of women that undergo mastectomy for breast cancer will choose to have reconstructive surgery performed to return the look and feel of healthy breast tissue. Common breast reconstruction techniques remove the pectoralis major and/or latissimus dorsi muscles from their skeletal attachments. This removal often leads to reductions in quality of life and self-reported shoulder function, but it is unclear how different breast reconstruction choices influence post-operative shoulder biomechanics.

The purpose of this dissertation was to explore the pathophysiological mechanisms contributing to the physical and psychosocial deficits experienced by breast reconstruction patients. Ultrasound shear wave elastography, robot-assisted measures of shoulder joint biomechanics, and patient-reported outcomes surveys were utilized to examine the long-term effects of various breast reconstruction approaches on the integrity of the shoulder joint and patients' self-reported physical and psychosocial well-being. Additionally, this dissertation includes a novel analysis of the neuromuscular compensation strategies adopted at the shoulder by breast reconstruction patients.

Results from this dissertation suggest that breast reconstruction approaches requiring the disinsertion of shoulder musculature may lead to long-term and potentially chronic deficits in shoulder strength and stiffness. Our results also suggest that objective measures of shoulder biomechanics are predictive of self-reported physical and psychosocial well-being. Additionally, this dissertation provides evidence that the underlying function of the pectoralis major muscle is

fundamentally altered following its disinsertion and the inclusion of radiotherapy. Finally, results from this dissertation suggest that patients who undergo bilateral breast reconstructions that disinsert the pectoralis major will adopt compensatory neuromuscular strategies only with their dominant arm.

Investigations included in this dissertation provide several novel and innovative insights into the peri-operative care of breast cancer patients. This dissertation contains the first ever investigation into the influence of mastectomy and breast reconstruction on the underlying integrity of the shoulder joint and pectoralis major muscle using both robotic-assisted measures of shoulder biomechanics and ultrasound shear wave elastography. We also utilize novel mediation analyses to establish a causal relationship between the breast reconstruction approach, its influence on shoulder biomechanics, and the effect these shoulder biomechanics have on patient-reported well-being. Finally, this dissertation includes the first ever investigation into how the otherwise intact central nervous system adapts to breast reconstruction procedures requiring the disinsertion of shoulder musculature. These insights pave the way for impactful future research into the relationship between functional shoulder joint biomechanics and breast cancer patient quality of life, as well as into the neuromuscular implications of mastectomy and breast reconstruction.

Findings from this dissertation have broad and significant clinical implications. This dissertation strengthens the surgical decision-making process for women choosing mastectomy and breast reconstruction. In particular, findings from this dissertation suggest that breast reconstructions requiring the disinsertion of shoulder musculature, in particular the combined disinsertion of shoulder musculature, should be avoided when possible. This dissertation also informs the development of optimal post-operative care. Specifically, that the restoration of shoulder adduction, abduction, internal rotation, and external rotation strength and adequate pectoralis major muscle function must be a focal point of post-operative care for patients undergoing mastectomy and breast reconstruction or breast-conserving therapy. Finally, findings from this dissertation apply to many clinical situations where musculature is surgically manipulated, such as in reconstructions of the head and neck using latissimus dorsi or serratus anterior muscle flaps or reconstructions of the lower extremity using rectus abdominis or gracilis muscle flaps.

Chapter 1. Introduction

1.1 Breast Cancer Management

Approximately 1.7 million women are diagnosed with breast cancer worldwide each year, which accounts for 12.7% of all new cancer cases[1]. In the United States, 260,000 women are diagnosed with breast cancer each year, and 1 in 8 women will be diagnosed with breast cancer at some point in their lifetime[2-4]. Fortunately, breast cancer mortality is at its lowest point in history. Over 90% of women diagnosed with breast cancer this year will live for at least 5 years, and 83% will live longer than 10 years[4]. This means a growing number of women will join the 3 million breast cancer survivors currently residing in the United States[4,5].

The standard of care for breast cancer depends on disease severity and includes a combination of systemic and/or localized treatments. Systemic treatments are introduced orally or intravenously and include endocrine therapy, targeted therapy, and chemotherapy[6]. Systemic treatments are used in order to minimize the risk of metastasis[6]. Localized treatments for breast cancer include radiotherapy and surgery. Radiotherapy can reduce the risk of recurrence for patients, particularly in women opting for breast conserving surgery[7]. Surgical interventions remove the tumor (lumpectomy or mastectomy) and assess the cancerous status of the lymphatic system (sentinel node biopsy or axillary lymph node dissection). In particular, a mastectomy surgically removes the entire breast tissue and is a clinically necessary procedure to manage moderate to severe breast cancer cases[8].

Mastectomy rates have increased in the United States over the past decade, with 30-60% of all women diagnosed with breast cancer undergoing a mastectomy[9-12]. Several reasons exist for this recent increase in the number of women opting for a mastectomy. First, women eligible for breast conserving therapy are instead opting for a more invasive mastectomy, with the number of these cases increasing by 34% between 2003 and 2011[13,14]. Second, genetic testing for breast cancer susceptibility via the BRCA1 and BRCA2 genetic mutations is more readily available[15]. The BRCA1 and BRCA2 mutations are connected with a ~30 and ~11 fold increase in breast cancer risk[15]. More women with a family history of breast cancer and an inherited BRCA genetic profile now opt for prophylactic mastectomy, with a 12% increase per year since 1998[16]. Finally, women diagnosed with unilateral breast cancer increasingly elect to perform a contralateral prophylactic mastectomy, which has increased 140% since 1998[16-21].

Mastectomy does not decrease breast cancer recurrence rates when compared to breast conserving therapy (e.g. lumpectomy and adjuvant radiation therapy), raising questions as to the factors most responsible for the recent uptick in mastectomy rate[17,22-24]. The availability of post-mastectomy breast reconstruction options to restore the look and feel of natural breast tissue could have an important role in the surgical decision making process for patients[11,25,26]. The rate of post-mastectomy breast reconstruction has increased as more women opt for a mastectomy[14,27-29]. Currently, ~63% of mastectomy patients will elect for a breast reconstruction surgery[28]. Mastectomy patients that undergo breast reconstruction exhibit improved cosmetic and psychosocial outcomes [30-36]. For example, breast reconstruction patients report improved appearance and psychosocial well-being when compared to mastectomy only patients.

There are various post-mastectomy breast reconstructions available to patients that account for differences in anatomy, desired cosmetic outcome, and cancer management plan. Breast reconstruction may be performed at the same time as a mastectomy (‘immediate’) or ~12 months after mastectomy (‘delayed’). All breast techniques require the removal of alternative soft tissues in order to replace the breast tissue removed during mastectomy. Immediate two-stage breast reconstruction is the most common technique, accounting for 68% of all reconstructions[37]. This reconstruction technique begins by releasing the pectoralis major from its attachments on the inferior/medial pole of the breast up onto the lateral border of the sternum, often referred to as the sternocostal fiber region. Next, a temporary tissue expander is placed underneath the muscle in the subpectoral space. Over several months, the tissue expander volume is increased until the chest wall can accommodate a permanent implant of the desired size. This volume expansion will stretch the remaining intact fibers of the pectoralis major. Finally, a second, far less invasive procedure will remove the tissue expander and place the permanent implant to recreate the breast mound.

Patients that require post-mastectomy radiotherapy are not candidates for immediate two-stage breast reconstruction. Radiotherapy will produce morbidity of the pectoralis major and skin, leading to increases in implant failure rates[38-41]. Therefore, post-mastectomy radiation therapy patients require a delayed procedure at least 12 months after mastectomy. An autologous tissue flap breast reconstruction is the preferred technique for these patients. Autologous tissue flaps are a collection of skin, adipose, and/or muscle tissue acquired from various locations on the body and relocated to the chest to perform the reconstruction. These autologous procedures use the tissue flap alone or a combination of the tissue flaps and implants to recreate the breast mound. A common autologous tissue for breast reconstruction is the deep inferior epigastric perforator flap (DIEP), which is a collection of blood vessels, skin, and adipose located in the lower abdomen[42,43]. Women with a high body mass index are good candidates for DIEP flap reconstructions as sufficient adipose tissue in the abdomen is required to perform the procedure. A DIEP flap recreates the breast mound from the adipose tissue of the flap rather than a permanent implant. During a DIEP flap breast reconstruction, the myocutaneous flap is transferred to the chest and its vasculature is reattached to a local blood supply via microsurgery. No abdominal or upper extremity musculature is disinserted during a DIEP flap breast reconstruction.

Another common autologous tissue used in irradiated mastectomy patients opting for breast reconstruction is the latissimus dorsi, which is a large, wide, flat, muscle located on the back (e.g. latissimus dorsi flap)[44-47]. Whereas DIEP flap reconstructions are used in women with a high body mass index, latissimus dorsi flap breast reconstruction is commonly used in women with a lower body mass index. During latissimus dorsi flap breast reconstructions, the muscle is fully disinserted from its origins on the iliac crest, thoracolumbar fascia, and thoracic spine before it is transposed anteriorly to the chest. A latissimus dorsi flap is often a two-stage procedure requiring the use of a tissue expander and permanent implant, with the expander and eventual implant placed either subpectorally (e.g. requiring the release of the pectoralis major) or prepectorally (e.g. the pectoralis major remains intact).

Breast reconstruction improves the quality of life and psychosocial well-being of breast cancer survivors[30-36,48-52]. However, outcomes differ depending on the breast reconstruction technique[53-55]. Latissimus dorsi flap patients experience significantly lower general satisfaction when compared to DIEP flap breast reconstruction patients,[54,55] but have similar satisfaction and quality of life to subpectoral implant patients[54]. Subpectoral implant breast reconstruction patients also self-report lower general satisfaction when compared to DIEP flap breast reconstruction patients. There is similar self-reported overall health in latissimus dorsi flap and subpectoral implant reconstruction patients when compared to mastectomy only patients more than 20 months post-operative[53,56,57]. This suggests that factors beyond the disinsertion of musculature alone are likely driving poorer psychosocial outcomes following latissimus dorsi and subpectoral implant reconstructions.

1.2 Biomechanical Consequences of Mastectomy and Breast Reconstruction

In addition to improved psychosocial well-being, post-mastectomy breast reconstructions were initially believed to result in minimal physical dysfunction[58-67]. However, subjective and quantitative investigations of shoulder function have since confirmed that breast reconstructions are not as innocuous as previously believed[59,68-71]. Investigations utilizing generalized physical function questionnaires have found that as many as 69% of latissimus dorsi flap patients will experience general discomfort, 58% will experience limitations in their ability to perform activities of daily living, 45% will experience deficits in range of motion, and 62% will experience weakness[68,72,73]. Similarly, following the disinsertion of the pectoralis major, patients are more likely to experience severe difficulty or the total inability to perform some activities of daily living[74,75]. The use of patient-reported outcomes surveys that focus specifically on upper extremity function confirms these functional deficits remain as many as 3 years following latissimus dorsi flap breast reconstruction and more than 2.5 years in subpectoral implant patients[76].

The intact pectoralis major and latissimus dorsi muscles contribute to force generation in shoulder adduction, flexion, extension, and internal rotation. Clinical examinations following latissimus dorsi flap and subpectoral implant breast reconstructions confirm that patients exhibit significantly reduced shoulder strength[62,72,77-80]. When compared to pre-operative levels, deficits in shoulder adduction, extension, and internal rotation are significantly reduced 7 years after latissimus dorsi flap breast reconstruction[59,72,78,80]. When compared to healthy individuals at least 3 years post-reconstruction, shoulder adduction, extension, and internal rotation are all significantly lower in latissimus dorsi flap patients[79]. When compared to scores obtained from healthy control participants, patients requiring the disinsertion of the pectoralis major exhibit significantly reduced shoulder strength in flexion, adduction, and external rotation[81]. When compared to the healthy arm, subpectoral implant participants exhibit significantly reduced shoulder strength in extension, adduction, and flexion[81,82]. These deficits remain when corrected for arm dominance.

Latissimus dorsi flap and subpectoral implant breast reconstructions can also restrict shoulder mobility. The most common shoulder mobility restrictions in latissimus dorsi flap and subpectoral implant breast reconstruction patients are flexion, abduction, and internal or external rotation [59,61,62,70,73,81,83-86]. Physician-led subjective examinations of shoulder mobility indicate that upward of 47% of patients exhibited shoulder range of motion deficits on their operated side when compared to their healthy limb[69]. When compared to control participants, participants previously treated with a pectoralis major flap exhibits significantly reduced abduction range of motion[86]. Interestingly, the latissimus dorsi and pectoralis major are not primary contributors to shoulder actions such as external rotation, suggesting that other factors contribute to range of motion deficits following these breast reconstruction techniques. One factor is the mastectomy itself. Following mastectomy, patients experience reduced shoulder flexion, abduction, and external rotation range of motion when compared to patients undergoing breast-conserving therapy[87]. Furthermore, when compared to mastectomy-only patients, latissimus dorsi flap patients exhibit similar shoulder range of motion[83,84].

Clinical assessments of the long-term effects of the disinsertion of the latissimus dorsi or pectoralis major indicate an enhanced risk of shoulder instability[59,86]. However, the accuracy and repeatability of clinical assessments of the shoulder are questionable[88-90]. Measurements of shoulder joint stiffness may serve as a valuable tool in the assessment of shoulder function following latissimus dorsi flap and subpectoral implant breast reconstructions because the latissimus dorsi and pectoralis major muscles are major contributors to shoulder joint stiffness[91-93]. However, no objective measures of shoulder stiffness have been obtained in any surgical breast cancer cohorts, including breast reconstruction patients. Shoulder stiffness can be quantified by measuring the impedance of the joint, which relates the change in joint angular position to the resultant change in joint torque[94-96]. Impedance can be measured in the time or frequency domain, and there are established methods to fit impedance in the frequency domain to a frequency response function. This frequency response function can be parameterized by approximating a second-order linear model to it with inertial (I), viscous (B), and stiffness (K) parameters[94-96]. The inertial parameter is relatively constant when the changes in shoulder angular position are small enough, as the mass of the arm is unchanged. The viscous and stiffness components change based on the measured torque response. Viscosity represents the velocity-dependent component of the equation, while stiffness represents the static component. The stiffness component is most closely related to clinical assessments of shoulder stability and is a valuable measure in understanding one's ability to execute activities of daily living, as many such activities destabilize the shoulder joint[97-99].

At rest, shoulder stiffness is maintained by the passive properties of soft tissues acting on the shoulder, such as ligament, tendon, and muscle[100]. During volitional contraction, shoulder stiffness is achieved almost entirely by the coordinated activations of muscles crossing the shoulder[100-102]. A significant limitation of shoulder stiffness measures is the inability to differentiate between the contributions of these individual tissues. Traditionally, examinations of the material properties, such as stiffness and elasticity, of individual tissues were limited to qualitative, manual palpation[103]. Recently, ultrasound shear wave elastography (SWE), a noninvasive imaging technique, has been used to estimate the material properties of individual tissues in vivo[104]. SWE utilizes an ultrasound transducer to generate acoustic radiation forces to induce shear waves within a soft tissue while simultaneously recording the resultant propagation velocity of these shear waves[105]. This shear wave velocity (SWV), when collected at rest and during contraction, provides insight into a given muscle's contribution to global joint function. This approach has been utilized in healthy populations to characterize changes in the material properties of muscle with changes in muscle length and contraction intensity[106-109]. Clinical populations, including patients with rotator cuff tears, have had the material properties of muscle assessed with SWE[110]. Shear wave elastography may serve as a valuable tool in assessing the impact of the disinsertion of the latissimus dorsi or pectoralis major on the contributions of remaining shoulder musculature to passive and active shoulder stiffness.

Several knowledge gaps exist regarding the mechanisms that drive patient-reported deficits and upper extremity morbidity following latissimus dorsi flap and subpectoral implant breast reconstructions. First, few studies have attempted to correlate subjective and quantitative measures, and those that have, have yielded contradictory results[72,79,111]. Second, most investigations into the effect of latissimus dorsi flap or subpectoral implant breast reconstructions on shoulder function provide poor control for covariates, such as radiotherapy and the additional disinsertion of the pectoralis major muscle. Following radiotherapy for breast cancer, patients may experience shoulder mobility deficits, stiffness, and fibrosis[40,112-115]. When compared to patients who had undergone mastectomy alone, patients who had undergone mastectomy combined with radiotherapy exhibit reduced shoulder flexion and abduction range of motion[116,117]. The pectoralis major contributes to shoulder flexion, adduction, and internal rotation, and its surgical removal can reduce the shoulder's range of motion, strength, and overall function[75,81,86]. Third, many investigations into the functional implications of latissimus dorsi flap and subpectoral implant breast reconstructions are limited to examinations of strength and range of motion, so it is unknown if the effects of these procedures extend to the stiffness of both the entire shoulder and the shoulder muscles surgically disinserted during breast reconstruction. Finally, clinical practice assumes that remaining, intact shoulder muscles increase their contributions to shoulder function in the absence of key shoulder muscles like the latissimus dorsi and pectoralis major[118]. Limited evidence suggests that the remaining, intact clavicular fiber region of the pectoralis major increases its contributions to shoulder function following subpectoral implant breast reconstruction[119]. The neuromuscular control of the shoulder is likely impacted, as several different treatments for breast cancer have been previously shown to reduce the muscle activity of the serratus anterior, rhomboid and upper trapezius muscles[120]. However, it is unclear how the other shoulder musculature adapts to the disinsertion of the latissimus dorsi and/or pectoralis major during post-mastectomy breast reconstruction procedures, and whether the remaining intact muscles can fully compensate for the lost functional from these muscles.

1.3 Purpose and Specific Aims

Currently, it appears that breast reconstructions requiring the disinsertion of shoulder musculature cause significant upper extremity dysfunction and alter postoperative quality of life. However, it is difficult to conclude from previous literature how breast reconstruction alter postoperative upper extremity function, as the inclusion of radiotherapy and the combined disinsertion of the pectoralis major and latissimus dorsi have not been controlled, and chronic neuromuscular adaptations have not been examined. The purpose of this dissertation was to improve the clinical understanding of how different breast reconstruction choices influence post-operative upper extremity biomechanics and patient quality of life. The five specific aims for this dissertation are:

Specific Aim #1: Determine how breast reconstruction choice and the inclusion of radiotherapy influence shoulder strength and stiffness. Patients previously treated with a subpectoral implant, latissimus dorsi flap, or deep inferior epigastric perforator flap breast reconstruction had novel robot-assisted measures of shoulder joint strength and stiffness assessed at least 18 months postoperatively. The disinsertion of the pectoralis major and/or latissimus dorsi and the inclusion of radiotherapy were both controlled by recruiting homogeneous experimental groups with respect to their cancer management. We tested the following hypothesis:

<u>Hypothesis 1</u>: *Breast reconstructions requiring the combined disinsertion of the latissimus dorsi and pectoralis major muscles will be associated with greater long-term shoulder morbidity when compared to subpectoral implant and deep inferior epigastric perforator breast reconstructions.*

Specific Aim #2: Examine the causal relationship linking breast reconstruction approach, shoulder joint strength and stiffness, and patient-reported physical and psychosocial well-being. Similarly to Specific Aim 1, we utilized experimental groups of patients previously treated with a subpectoral implant, latissimus dorsi flap, or deep inferior epigastric perforator flap breast reconstruction. In addition to robot-assisted measures of shoulder joint strength and stiffness, patients also completed self-reported measures of upper extremity function, shoulder pain and disability, and general physical and psychosocial well-being at least 18 months postoperatively. Novel mediation analyses explored the causal relationship between the breast reconstruction approach, its influence on shoulder biomechanics, and the influence those shoulder biomechanics have on patient-reported physical and psychosocial well-being. We tested the following hypotheses:

Hypothesis 2a: Breast reconstructions requiring the combined disinsertion of the latissimus dorsi and pectoralis major will be associated with greater deficits in self-reported physical and psychosocial well-being when compared to subpectoral implant and DIEP flap breast reconstructions.

Hypothesis 2b: Objective measures of shoulder joint function will be predictive of self-reported physical and psychosocial well-being.

Specific Aim #3: Determine how subpectoral implant breast reconstruction influences shoulder joint and pectoralis major function. It is unclear how the disinsertion of the sternocostal fiber region of the pectoralis major during subpectoral implant breast reconstruction influences the function of the remaining muscle volume or the shoulder joint. Biomechanical assessments of shoulder strength and stiffness and ultrasound shear-wave elastography based measures of pectoralis major material properties were obtained from patients treated with subpectoral implant breast reconstruction at least 18 months prior and healthy, age-matched control participants. We tested the following hypotheses:

Hypothesis 3a: Subpectoral implant breast reconstruction participants will exhibit significantly reduced shoulder strength and stiffness when compared to healthy, age-matched control participants.

Hypothesis 3b: Subpectoral implant breast reconstruction participants will exhibit increased shear wave velocity in the clavicular fiber region of the pectoralis major when compared to healthy participants.

Specific Aim #4: Examine how mastectomy and subpectoral implant breast reconstruction or breast-conserving therapy influence pectoralis major function. An increasing number of women eligible for breast-conserving therapy are voluntarily electing to undergo mastectomy and breast reconstruction. Breast-conserving therapy influences the material properties of the pectoralis major at rest, whereas mastectomy and subpectoral implant breast reconstruction influence the material properties of the pectoralis major during volitional shoulder torque generation. We assessed the material properties of the fiber regions of the pectoralis major during the generation of shoulder torques in patients previously treated with breast-conserving therapy or subpectoral implant breast reconstruction and healthy, age-matched control participants. We then tested the following hypotheses:

Hypothesis 4a: Subpectoral implant breast reconstruction participants will exhibit increased shear wave velocity in the clavicular fiber region of the pectoralis major when compared to breast-conserving therapy patients and healthy participants.

Hypothesis 4b: Breast-conserving therapy patients will exhibit significantly lower pectoralis major shear wave velocity when compared to healthy participants and subpectoral implant breast reconstruction participants.

Specific Aim #5: Determine how remaining, intact shoulder musculature compensate following subpectoral implant breast reconstruction. Clinical practice assumes that remaining, intact shoulder musculature will increase their contributions to shoulder function following the disinsertion of the shoulder muscles during post-mastectomy breast reconstruction. However, this has never been empirically measured. Neuromuscular coordination was assessed more than 3 years post-operatively in patients treated bilaterally with mastectomy and subpectoral implant breast reconstruction and healthy controls. Surface electromyography were obtained from 16 superficial shoulder muscles bilaterally while participants generated 8 three-dimensional shoulder torques in 5 arm postures. We tested the following hypotheses:

<u>Hypothesis 5a</u>: *Following the disinsertion of the sternocostal fiber region of the pectoralis major, bilateral subpectoral implant breast reconstruction patients will exhibit altered surface EMG activation amplitudes when compared to healthy participants, regardless of arm dominance.*

<u>Hypothesis 5b</u>: *Subpectoral implant patients will also adopt unique neuromuscular compensation strategies at the shoulder, as evidenced by altered muscle synergy structure, regardless of arm dominance.*

<u>Hypothesis 5c</u>: *Neuromuscular complexity will be reduced in subpectoral implant breast reconstruction patients on both the dominant and non-dominant arms.*

1.4 Organization of Dissertation

This dissertation consists of seven chapters and one appendix. Chapters 2 through 6 represent full-length manuscripts either accepted or prepared for publication in peer-reviewed journals. Chapter 2 examines the influence of breast reconstruction approach on long-term shoulder morbidity. Chapter 3 explores the causal relationship linking breast reconstruction approach to functional shoulder biomechanics, and functional shoulder biomechanics to patient-reported quality of life. Chapters 4 and 5 assess the influence of mastectomy and subpectoral implant breast reconstruction or breast conserving therapy on functional shoulder biomechanics and pectoralis major function. Chapter 6 examines the neuromuscular compensation strategies adopted by bilateral subpectoral implant breast reconstruction patients in order to maintain adequate shoulder function. Finally, Chapter 7 discusses the strengths, weaknesses, and significance of this dissertation, summarizes its results and conclusions, and provides guidance and suggestions for future research, respectively. Appendix A provides supplemental material for Chapters 2 through 6 which includes detailed statistical model results.

Chapter 2. The Influence of Reconstruction Choice and Inclusion of Radiotherapy on Functional Shoulder Biomechanics in Women Undergoing Mastectomy for Breast Cancer

The following chapter was published in *Breast Cancer Research and Treatment,* and all images contained in this chapter are copyrighted by Elsevier. Please refer to the following publication when referencing this work: Leonardis JM, Diefenbach BJ, Lyons DA, Olinger TA, Giladi AM, Momoh AO, Lipps DB. The Influence of Reconstruction Choice and Inclusion of Radiation Therapy on Functional Shoulder Biomechanics in Women Undergoing Mastectomy for Breast Cancer. Breast Cancer Research and Treatment. 2019;173(2):447-53.

2.1 Abstract

The functional implications of reconstructing the breast mound with a latissimus dorsi (LD) flap or placing an implant under the pectoralis major (PM) muscle is complicated by potential co-morbidities from disinserting these muscles and adjuvant radiotherapy. We utilized novel robot-assisted measures of shoulder stiffness and strength to dissociate how breast reconstruction choice and inclusion of radiation therapy impact shoulder morbidity in post-mastectomy reconstruction patients. Shoulder strength and stiffness were collected from 10 irradiated LD flap breast reconstruction patients, 14 two-stage subpectoral implant reconstruction patients (subpectoral), and 10 irradiated deep inferior epigastric perforator (DIEP) flap patients an average of 659 days post-reconstruction. Univariate ANOVAs examined surgical group differences in strength and stiffness. There were main effects of surgical group on vertical adduction, vertical abduction, and internal rotation strength. The LD flap group was significantly weaker than the subpectoral group in all measures and significantly weaker than the DIEP group during vertical adduction. There was also a main effect of surgical group on vertical adduction stiffness, where the LD group exhibited

significantly reduced stiffness while producing vertical adduction torque. No significant differences between the subpectoral and DIEP groups existed for any measure of shoulder strength or stiffness. Disinsertion of the LD, not the disinsertion of the PM or radiotherapy, contributes to strength deficits following LD flap breast reconstructions. The combined disinsertion of the PM and LD compromises shoulder stability in the vertical plane. Shoulder function should be a focal point of the surgical decision-making process and post-operative care.

2.2 Introduction

Increasing mastectomy rates have been driven in part by more breast cancer patients opting for bilateral mastectomy with reconstruction, with approximately 107,000 post-mastectomy breast reconstruction surgeries performed in the U.S. annually [121]. Patients that undergo mastectomy without reconstruction can experience psychosocial disturbances and problems with body image and sexuality [122]. A breast reconstruction procedure restores the form, appearance, and feel of the breast mound [123] and provides psychosocial and quality of life benefits [124]. Identifying the functional implications of mastectomy and breast reconstruction is needed to optimize the quality of life of breast reconstruction patients, given the increasing survivorship with advances in early detection and therapy [125].

Various breast reconstruction procedures are available to mastectomy patients to restore the breast mound [16,28,126]. An immediate two-stage implant-based breast reconstruction accounts for ~60% of all post-mastectomy reconstructions [127]. This procedure disinserts the pectoralis major (PM) from the ribs and lower sternum to accommodate a subpectoral tissue expander and eventual implant. Because implant reconstructions have relatively high failure rates after radiation therapy [128-130], the latissimus dorsi (LD) is used as a myocutaneous flap in combination with expanders and implants to restore the breast mound for post-mastectomy patients after radiation therapy [91].

This procedure fully disinserts the LD from the spine and transposes the flap to the chest for additional tissue coverage of an implant. The PM muscle can also be disinserted during LD breast reconstruction for implant coverage with both muscle flaps. Alternatively, irradiated patients can be reconstructed with a deep inferior epigastric perforator (DIEP) flap. The DIEP flap recreates the breast mound without an implant by transferring the abdominal tissue to the chest and using microsurgical anastomotic techniques to reestablish blood supply to the flap. A DIEP flap reconstruction requires minimal division of PM fibers over the 3rd or 4th rib near the sternum to access the internal mammary recipient vessels but does not include disinsertion of any shoulder muscles.

Disinsertion of the PM and/or LD can have long-term functional consequences for patients undergoing mastectomy with breast reconstruction. These muscles are critical for maintaining healthy shoulder joint stability and have similar functional demands, including shoulder adduction and internal rotation [61,62,72,91,118,131,132]. The disinsertion of both muscles produces strength and mobility deficits in up to half of all LD flap patients [59,61,62,68,69,72,78,80,83,133-135]. LD flap patients also self-report shoulder instability, even in the absence of strength or mobility deficits[59]. Since reduced stability negatively impacts quality of life [97,136,137], objective measures of shoulder stability following breast reconstruction can provide new insights to improved surgical decision-making and post-operative care. Furthermore, the functional implications of the inclusion of post-mastectomy radiation therapy on the treated shoulder of reconstruction patients is unclear, as patients undergoing radiotherapy and mastectomy can exhibit reduced mobility and strength [116,117].

The objective of this study was to determine how breast reconstruction choice influences the long-term functional integrity of the shoulder joint using objective robot-assisted measures of shoulder joint stability (‘stiffness’) and strength. LD flap reconstruction patients were compared to subpectoral implant reconstruction patients and DIEP flap patients to control for the effects of additional release of the PM and radiation therapy, respectively. We hypothesized that LD flap patients would exhibit significantly reduced strength and active stiffness in vertical adduction when compared to both the two-stage implant and DIEP flap patients.

2.3 Methods

Participants

A retrospective medical chart review from a single surgeon's practice retrospectively identified 155 women eligible for this study, of which 34 women consented to participate in a single experimental session (Table 2.1). We examined women undergoing one of three post-mastectomy breast reconstruction procedures: subpectoral implant, LD flap, and DIEP flap. Fourteen patients underwent an immediate two-stage subpectoral implant with the PM muscle elevated during surgery, but did not require radiation therapy. Ten LD flap patients and 10 DIEP flap patients that required radiation therapy underwent delayed breast reconstruction in order to complete radiation therapy prior to their reconstructive surgery. The LD flap patients had an implant reconstruction where both the LD muscle and PM muscle were elevated during surgery. The DIEP flap patients had an autologous reconstruction that did not require any upper extremity muscles to be elevated during surgery. A minimum of 12 months was required after completion of breast reconstruction before biomechanical assessments The University of Michigan's Institutional Review Board approved all study procedures (HUM00114801) and participants provided written informed consent prior to data collection. Participants with previous neuromuscular or orthopaedic disorders affecting the upper limb were excluded from the study.

Experimental Setup

Participants were secured to an adjustable chair (Biodex Medical Systems, Shirley, New York) with torso movement restricted using a chest strap and cushioned plates positioned along the lower back and sides. A custom-made plastic cast extending from the hand to the shoulder attached the participant's examined shoulder to a computer-controlled brushless servomotor (Baldor Electric Company, Fort Smith, AR) (Figure 2.1). Within the cast, the elbow was fixed at 90° and the wrist was neutral. Movement of the scapula was not restricted. The center of rotation of the glenohumeral joint was aligned to the motor's axis of rotation. Shoulder joint torques were measured using a six degrees-of-freedom load cell (JR3, Inc., Woodland, CA) attached between the crank arm of the motor and the cast. Our measurement coordinate system was defined using established biomechanical standards[138].

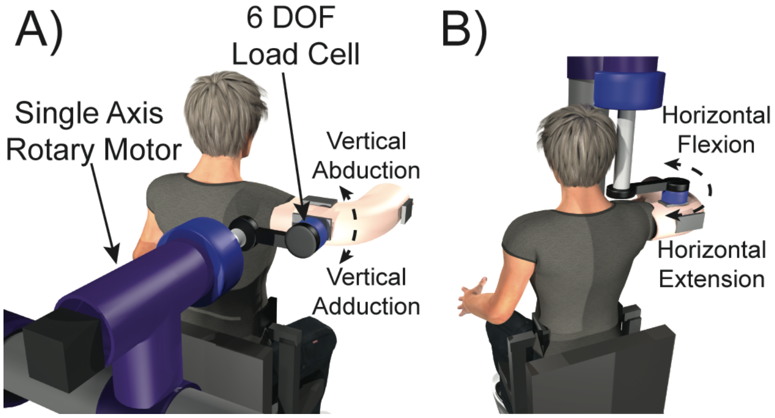

Figure 2.1 Schematic of experimental setups. A single-axis rotary motor perturbed a participant's examined shoulder in while a six-degree-of-freedom load cell measured resultant torques in all three dimensions. Visual feedback was provided via LCD screen. (A) The rotary motor was positioned to move the arm in the vertical plane while participants were relaxed or generating shoulder torques in vertical adduction (downwards) or vertical abduction (upwards). (B) The rotary motor was positioned to move the arm in the horizontal plane while participants were relaxed or generating shoulder torques in horizontal flexion (forward) or horizontal extension (backwards).

Experimental Protocol

Participants performed maximal voluntary contractions (MVC) in the positive and negative directions of each measurement plane (vertical adduction/abduction; internal/external rotation; horizontal flexion/extension) at the beginning of the experiment to measure and normalize the remaining trials to each participant's strength. Participants were then examined in two separate shoulder planes of motion (vertical adduction/abduction or horizontal flexion/extension) in a random order (Figure 2.1). The shoulder remained in the same posture in all trials.

The stiffness of the shoulder joint was measured in each plane by measuring the resultant shoulder torque as the motor applied a series of small, stochastic perturbations with a pseudo-random binary sequence (0.06 radian amplitude and 150 millisecond switching interval). Each perturbation trial lasted for 60 seconds, during which the participants were asked to remain relaxed (0% MVC) or to maintain a constant torque scaled to ±10% MVC for the given direction. Participants used visual feedback to assist in maintaining the prescribed torque. One passive trial was included at the beginning of each motor configuration to acclimate the participants to the sensation of being perturbed. We repeated each perturbation testing condition for six total trials per motor configuration and then repeated these procedures for the remaining motor configuration. In total, each participant performed 14 perturbation trials.

Data and Statistical Analysis

Shoulder stiffness was estimated using system identification [94,139] using MATLAB (v2016a, Mathworks, Inc, Natick, MA, USA). For each trial, we first measured joint impedance by measuring the dynamic relationship between imposed change in joint angle in a given plane and the resultant torque [96]. Joint impedance was quantified as a frequency response function from

0 – 10 Hz. A numerical optimization parameterized this frequency response function using a 2nd order linear system consisting of inertial (*I)*, viscous (*B)*, and stiffness (*K)* components[139]. The current study only reports the stiffness component as this is the most clinically relevant parameter for assessing the stability of the shoulder joint.

All statistical procedures were performed in SPSS (v24, IBM Corporation, Chicago, IL, USA). The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request. Differences in demographic measures (age, height, mass, BMI, days post-reconstruction surgery) between each experimental group (LD flap vs. subpectoral; LD flap vs. DIEP) were investigated using t-tests. We tested our hypothesis that the LD flap group would exhibit reduced shoulder strength and stiffness in the vertical plane when compared to the subpectoral group and DIEP groups using univariate ANOVAs. Our outcome measures were strength in one of six directions (vertical adduction, vertical abduction, horizontal flexion, horizontal extension, internal rotation, external rotation) and stiffnesses in two different directions (vertical and horizontal) and three different activation conditions (at rest, adduction/flexion, and abduction/extension). Surgical group (subpectoral implant, LD flap or DIEP flap) was a fixed factor. Bonferroni-corrected multiple comparisons were used to analyze significant main effects. All analyses utilized a significance level of $p<0.05$. Effect sizes (partial η^2) were calculated to distinguish between small (0.010-0.059), moderate (0.060-0.0139), and large (≥0.140) clinically relevant differences [140].

2.4 Results

Demographics

Patient demographics are shown in Table 2.1. There were no significant differences in age, height, weight, BMI, or days post-reconstruction between the LD flap group and either the subpectoral or the DIEP flap groups.

Table 2.1 Mean (standard error) participant demographics for each of the three experimental groups: latissimus dorsi flap (LD Flap), two-stage subpectoral implant (Subpectoral), and deep inferior epigastric perforator flap (DIEP Flap).

				LD vs. Subpectoral	LD vs. DIEP
	LD Flap	Subpectoral	DIEP	p	p
Number of Participants	10	14	10		
Age (yrs)	53 (3.3)	49 (2.5)	51 (2.8)	.310	.607
Height (m)	1.62 (.01)	1.64 (.01)	1.65 (.02)	.221	.201
Weight (kg)	75 (5.3)	71 (2.9)	84 (5.6)	.534	.236
BMI (kg/m^2)	29 (1.9)	26 (1.1)	31 (2.2)	.325	.425
Days Post-Operative from Reconstruction	670 (44)	588 (41)	788 (81)	.186	.224
Dominant/Non-Dominant Limb	7/3	10/4	5/5		
Radiation Therapy (Yes/No)	10/0	0/14	10/0		
Chemotherapy (Yes/No)	8/2	5/9	8/2		
Axillary Lymph Node Dissection (ALND)	3	0	4		
Sentinel Lymph Node Biopsy (SLNB)	4	12	4		
ALND + SLNB	3	0	0		

Shoulder Strength

There was a significant main effect of surgical group on vertical adduction ($F_{2,33}=6.326, p=0.005, \eta^2=0.28$), vertical abduction ($F_{2,33}=4.047, p=0.021, \eta^2=0.20$), and internal rotation strength ($F_{2,33}=4.316, p=0.022, \eta^2=0.21$) (Figure 2.2). Post hoc comparisons revealed that during vertical adduction, the LD flap group was 22.7% weaker than the subpectoral group ($p=0.009$) and 23.5% weaker than the DIEP flap group ($p=0.014$). Furthermore, the LD flap group was 20.0% weaker than the subpectoral group ($p=0.044$) during vertical abduction. The LD flap group was also 19.2% weaker than the subpectoral group during internal rotation ($p=0.034$). The subpectoral and DIEP flap groups did not differ (all $p>0.99$). No significant differences were observed between the groups for horizontal flexion ($F_{2,33}=0.815, p=0.451, \eta^2=0.05$), horizontal extension ($F_{2,33}=2.649, p=0.086, \eta^2=0.14$), or external rotation ($F_{2,33}=0.691, p=0.508, \eta^2=0.04$) strength.

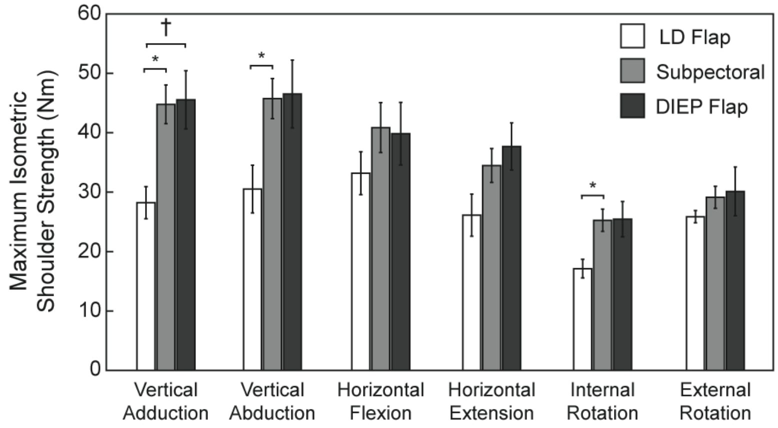

Figure 2.2 Mean shoulder strength across three reconstructive surgeries. Participants performed maximal isometric shoulder torques in the positive and negative directions in the vertical (vertical adduction, vertical abduction), horizontal (horizontal flexion, horizontal extension), and rotation planes (internal rotation, external rotation). Bars represent mean ± standard isometric shoulder strength (Nm) error for each experimental group (LD: latissimus dorsi flap; Subpectoral: two-stage subpectoral implant; DIEP: deep inferior epigastric perforator flap). * denotes significant difference between the LD and implant groups. † denotes significant difference between the LD and DIEP groups.

Shoulder Stiffness

There was a significant main effect of surgical group on shoulder stiffness as participants produced vertical adduction torque (*$F_{2,33}=5.655$, $p=0.008$, $\eta^2=0.27$*) (Figure 2.3). Post hoc analyses revealed that during this condition, the LD flap group exhibited 24.6% lower shoulder stiffness than the DIEP group (*$p=0.01$*). Although the LD flap participants experienced a greater volume of muscle disinsertion than the subpectoral group, the groups were not significantly different while producing vertical adduction (*$p=0.721$*) torque. No significant differences were observed between the groups when producing vertical abduction (*$F_{2,33}=0.995$, $p=0.381$, $\eta^2=0.06$*), horizontal flexion (*$F_{2,33}=0.597$, $p=0.557$, $\eta^2=0.04$*), or horizontal extension (*$F_{2,33}=1.002$, $p=0.379$, $\eta^2=0.06$*) torques. All three experimental groups also exhibited similar shoulder stiffness at rest in the vertical (*$F_{2,33}=1.034$, $p=0.367$, $\eta^2=0.06$*) and horizontal planes (*$F_{2,33}=0.096$, $p=0.908$, $\eta^2=0.01$*).

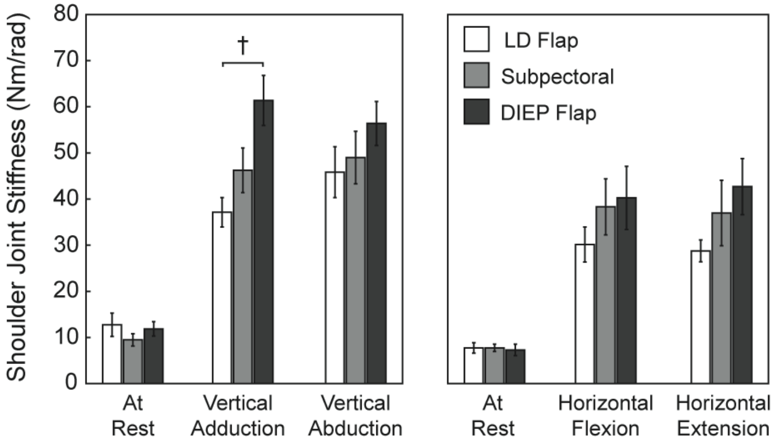

Figure 2.3 Mean shoulder stiffness across three reconstructive surgeries. Participants were perturbed in the vertical (A) and horizontal (B) planes of motion. During perturbation trials, participants were asked to remain relaxed (While at Rest) or to maintain torques scaled to -10% MVC (vertical/horizontal flexion) and +10% MVC (vertical/horizontal extension) in the respective planes of motion. Bars represent mean ± standard error shoulder stiffness (Nm/rad) for each experimental group (LD: latissimus dorsi flap; Subpectoral: two-stage subpectoral implant; DIEP: deep inferior epigastric perforator flap). † denotes significant difference between the LD and DIEP groups.

2.5 Discussion

This study dissociated the effects of reconstruction choice and the inclusion of radiation therapy in women with breast cancer that undergo mastectomy and reconstruction. Our results provide the first objective evidence that LD flap reconstructions diminish shoulder stability. Irradiated patients that have the PM disinserted during a LD flap reconstruction exhibited significantly reduced active shoulder stability in vertical adduction when compared to irradiated DIEP flap patients who had no muscle disinsertion. Our results also indicate that the disinsertion of the LD and PM leads to greater overall shoulder strength deficits than the disinsertion of the PM alone during a standard two-stage breast reconstruction. Finally, the combined disinsertion of the LD and PM in irradiated patients reduces shoulder strength when compared to irradiated DIEP flap patients with no further muscle disinsertion. These results confirm that LD flap reconstruction patients experience worse long-term shoulder morbidity than other breast reconstruction patients, and that post-operative interventions are needed to restore shoulder strength and stability in LD flap patients. Our results also suggest that the combined disinsertion of the PM and LD should be avoided when it is possible to complete the procedure utilizing the LD alone.

Objective measures of shoulder strength provide insights into the degree of impairment following LD flap reconstruction. Prior investigations of functional outcomes in LD flap reconstruction focus on the first 12 months post-reconstruction, when the acute effects of the surgery are present [61,62,68,69,78,134,141]. Only three prior studies have directly measured shoulder strength greater than 6 months post-reconstruction. When compared to pre-surgical levels and the non-operated shoulder, shoulder vertical adduction, extension, and internal rotation strength remains reduced more than 4 years post-LD flap breast reconstruction [59,72]. When compared to healthy controls, LD flap patients suffer from reduced isometric shoulder adduction, extension, and internal rotation strength 3.5 years post-reconstruction and radiotherapy [79]. Our findings agree with previous reports that LD flap reconstructions compromise shoulder strength. We found the LD group exhibited reduced strength when compared to the subpectoral group, who underwent disinsertion of the PM but no adjuvant radiotherapy, and the DIEP group, who had adjuvant radiotherapy. This supports prior observations that strength loss observed following LD flap breast reconstructions is more related to the loss of the latissimus dorsi than radiotherapy [79].

Our study used novel assessments of shoulder stiffness to measure the mechanical stability of the shoulder joint following breast reconstruction. These stiffness measures quantify a patient's ability to stabilize their arm [136] and provide insights into the health and function of the shoulder during activities of daily living. At rest, stiffness quantifies the stability provided by passive soft tissues acting on the shoulder, such as ligament, tendon, and muscle [100]. All surgical groups exhibited similar measures of stiffness at rest in both the vertical and horizontal planes. These results are unsurprising, as muscle constitutes a small contribution to overall joint stiffness at rest [100]. Under active conditions, shoulder stiffness is largely attributable to the coordinated activations of shoulder muscles [100,102,142]. We observed altered active joint stiffness during vertical adduction following disinsertion of the LD. This reduction in stiffness is likely due to the combined disinsertion of the LD and PM, as the subpectoral and LD flap groups exhibited similar stiffnesses during vertical adduction. These results agree with previous reports of reduced stability following the disinsertion of the LD [59].

Clinical practice assumes that the musculoskeletal system can adapt and compensate for lost function following muscle disinsertion in reconstructive surgery [118,143-145]. The LD and PM are two of three muscles that contribute significantly to shoulder vertical adduction. Therefore, the disinsertion of both muscles leaves little room for compensation in vertical adduction from intact musculature . The LD also contributes substantially to shoulder horizontal extension, and therefore its disinsertion should theoretically influence horizontal extension stiffness. However, our LD flap group exhibited similar horizontal extension stiffness to both the subpectoral and DIEP flap groups, suggesting an increased contribution from remaining musculature. The teres major, infraspinatus, and subscapularis muscles, which contribute to shoulder stability using similar lines of action as the latissimus dorsi when the arm is abducted to 90° [91], are the most likely muscles to compensate. Additionally, the intact clavicular fiber region of the PM contributes to shoulder function in the horizontal plane [146].

Our study has certain limitations. First, our cross-sectional study design does not allow for the longitudinal effects of LD flap breast reconstructions to be fully appreciated. We mitigated this limitation by using well-defined control groups to control for the disinsertion of the PM and the inclusion of radiation therapy. Theoretically, the opposite shoulder could serve as a control for each patient. However, experimental time constraints and variability in arm dominance, history of injury to the opposite arm/shoulder, and patient preference for completing unilateral or bilateral surgeries made it difficult to use the opposed shoulder as a true control. Our experimental procedures only assessed the shoulder in a single posture, but the chosen posture should illicit the greatest contributions of the PM and LD to shoulder function based on their moment arms [147]. The LD was fully disinserted from the spine in all LD patients, but there might have been variability in the amount that the PM was disinserted for each participant. We attempted to minimize this variability by recruiting patients from a single surgeon. The vast majority of patients included in the current study received radiation therapy from outside providers, and therefore we had limited access to their radiation therapy records. We were only able to control for the inclusion of radiotherapy in their management of breast cancer, and could not control for radiation dose or field design.

2.6 Conclusions

In conclusion, we demonstrated that the disinsertion of the LD, not the disinsertion of the PM muscle or radiotherapy, contributes to the commonly observed strength deficits following LD flap breast reconstruction. Our findings also provide objective evidence that the combined disinsertion of the PM and LD compromises LD flap patients ability to stabilize their shoulder joint in the vertical plane. When possible, consideration should be given to harvesting only the LD for coverage of implants as opposed to the LD and PM. Together, these findings suggest that shoulder function should be included in the surgical decision-making process and that post-operative care should aim to improve both shoulder strength and stability.

Chapter 3. The Influence of Functional Shoulder Biomechanics as a Mediator of Patient Reported Outcomes Following Mastectomy and Breast Reconstruction

The following chapter was published in *Plastic and Reconstructive Surgery,* and all images contained in this chapter are copyrighted by Lippincott, Williams, and Wilkins. Please refer to the following publication when referencing this work: Leonardis JM, Lyons DA, Giladi AM, Momoh AO, Lipps DB. The Influence of Functional Shoulder Biomechanics as a Mediator of Patient Reported Outcomes Following Mastectomy and Breast Reconstruction. Plastic and Reconstructive Surgery. In Press.

3.1 Abstract

Post-mastectomy breast reconstruction techniques differentially influence patient-reported physical and psychosocial well-being. Objective measures of shoulder biomechanics, which are uniquely influenced by reconstruction technique, may provide insight into the influence of reconstruction technique on patient-reported outcomes. Robot-assisted measures of shoulder strength and stiffness, and patient-reported outcomes surveys (PROMIS-UE, SPADI, QuickDASH, SF12-PCS, SF12-MCS) were obtained from 46 women who had previously undergone mastectomy and a combined latissimus dorsi flap + subpectoral implant (LD + subpectoral implant), subpectoral implant, or DIEP flap breast reconstruction. Mediation analyses examined the role of functional shoulder biomechanics as a mediator between reconstruction technique and patient-reported outcomes. Reconstruction technique uniquely affected shoulder biomechanics, with LD+subpectoral implant patients exhibiting reduced shoulder strength and stiffness compared to subpectoral implant and DIEP flap patients. Increasing external rotation strength was predictive of increasing PROMIS-UE score (*p=0.04*), indicating improved upper extremity function. Increasing shoulder stiffness while at rest was predictive of increasing

QuickDASH score (*p=0.03*), indicating worsened upper extremity function, while increasing stiffness at rest and during contraction was indicative of decreasing SF12-MCS score (all *p≤0.02*), indicating worsened psychosocial well-being. Reconstruction technique did not predict any survey score directly (all *p≥0.06*), or when mediated by functional shoulder biomechanics (all *p≥0.24*). In the current cohort, LD+subpectoral implant breast reconstructions significantly reduced shoulder strength and stiffness when compared to the other techniques. Additionally, objective measures of shoulder biomechanics were predictive of patient-reported physical and psychosocial well-being. Our results emphasize the need for improved peri-operative screening for shoulder functional deficits in patients undergoing breast reconstruction.

3.2 Introduction

Women treated for primary breast cancer increasingly opt for breast reconstruction after mastectomy procedures [28]. Approximately 68% of women who pursue post-mastectomy breast reconstruction undergo implant reconstruction [126]. In addition to traditional subpectoral implant techniques, reconstructive options include latissimus dorsi flap (LD) or free tissue transfer procedures such as the deep inferior epigastric perforator (DIEP) flap. These options involve various degrees of muscle disinsertion or muscle fiber division. Alterations to muscle group(s) that are principal stabilizers of the shoulder have potential ramifications for postoperative function.

Post-mastectomy breast reconstruction affords many quality of life benefits over mastectomy alone, including improved patient satisfaction with the breasts, sexual well-being, and psychosocial outcomes [30,31,50,148]. However, different approaches to breast reconstruction may influence patient-reported quality of life. For instance, patients who have undergone LD and subpectoral implant reconstructions report lower general satisfaction and physical well-being when compared to patients reconstructed with a DIEP flap[149-151]. Patients with LD reconstruction also report general discomfort, difficulty performing activities of daily living, upper extremity weakness, and reduced shoulder range of motion at greater rates than patients with a subpectoral implant or DIEP flap reconstructions [68,72,141]. These patient-reported functional deficits after LD breast reconstruction may persist up to 3 years post-reconstruction [76,79].

Objective measures of shoulder biomechanics may provide greater insight into the role of breast reconstruction technique on patient-reported outcomes related to the shoulder and upper extremity. In LD patients, decreasing shoulder strength is significantly correlated with patient-reported upper extremity dysfunction [79]. Similarly, decreasing shoulder strength and stability has been linked to increasing patient-reported shoulder pain and disability in subpectoral implant patients [152]. Little evidence linking shoulder biomechanics and patient-reported outcomes exist in patients DIEP flap breast reconstruction. It remains unclear if diminished patient-reported well-being is directly influenced by the breast reconstruction technique itself, or rather through the indirect effects that many breast reconstruction techniques have on shoulder biomechanics. Therefore, the purpose of this study was to examine the influence of precise measures of shoulder biomechanics as potential mediators in the relationship between breast reconstruction technique, shoulder and upper extremity function, and patient-reported well-being. We hypothesized that the reconstruction technique utilized would directly influence shoulder biomechanics, which in turn would directly influence patient-reported physical and psychosocial well-being.

3.3 Methods

Women who had previously undergone post-mastectomy breast reconstruction at the University of Michigan between 2014 and 2016 were identified. In order to minimize variability across procedure types and techniques, participants were recruited from a single surgeon's practice (A.O.M.). Patients included had undergone post-mastectomy breast reconstruction of one or both breasts with one of the following techniques: LD + subpectoral implant, subpectoral implant, or DIEP flap breast reconstruction. A minimum of 12 months from the final breast reconstruction procedure was required for inclusion. Patients with prior orthopedic or neurologic injuries affecting the upper extremity were excluded. Also excluded were women with previously failed breast reconstructions and women who received subpectoral breast augmentations prior to mastectomy and reconstruction. Demographic and clinical data were collected through a review of the electronic medical record.

LD + subpectoral implant reconstructions in this patient population involved both the disinsertion of the origin of the latissimus dorsi muscle from the spinous processes and the disinsertion of the origin of the pectoralis major at the inferior/medial pole of the breast up onto the lateral border of the sternum. A similar disinsertion of the pectoralis major muscle, along with the use of acellular dermal matrix for inferior pole coverage, was performed in all subpectoral implant patients. DIEP flap patients had pectoralis muscle fibers over the cartilaginous segment of the 3rd or 4th ribs divided to gain access to the internal mammary vessels but did not require disinsertion from skeletal origins or insertions.

The University of Michigan's Institutional Review Board approved all study procedures (HUM00114801). Eligible patients were first contacted via letter and followed up by phone a minimum of 10 days after the letter was mailed. Written informed consent was obtained from all participants at the beginning of the experimental session, prior to the collection of any data. Study participants received a nominal stipend to offset any costs incurred by patients due to their participation in this study.

Patient-Reported Outcomes

Five validated patient-reported outcomes instruments (PROs) were utilized in order to assess the influence of post-mastectomy breast reconstruction technique and functional shoulder biomechanics on psychosocial and health-related quality of life. The Shoulder Pain and Disability Index (SPADI) provides insight into shoulder pain and function during the execution of activities of daily living [153]. A higher SPADI score indicates worse pain and disability. The abbreviated version of the Disabilities of the Arm, Shoulder and Hand Score (QuickDASH), measures physical function and symptoms experienced by people with any or multiple musculoskeletal disorders of the upper limb, whereby higher scores indicate worsened physical function experienced within the previous 7 days [154]. The Patient Reported Outcome Measurement Information Survey (PROMIS) Upper Extremity (UE) Instrument measures upper extremity function in adults. Higher PROMIS-UE scores represent improved overall upper extremity function [155]. The 12-item Short Form Survey Physical (SF12-PCS) and Mental Composite (SF12-MCS) scores provide insight into a patient's general physical and psychosocial well-being over the previous 4 weeks [156]. Increasing SF12-MCS/PCS scores indicate improved physical and psychosocial quality of life. Patients completed these surveys digitally (Qualtrics, SAP, Walldorf, DE) within one week of the experimental session.

Functional Shoulder Biomechanics

At the onset of experimental procedures, study participants were secured to an adjustable chair (Biodex Medical Systems, Shirley, New York) that restricted torso movement using a cushioned chest strap and padded side plates (Figure 3.1). A plastic, removable cast attached the participant's examined shoulder to a computer-controlled brushless rotary motor (Baldor Electric Company, Fort Smith, Arkansas), where the center of rotation of the glenohumeral joint was aligned to the motor's axis of rotation. The cast extended from the shoulder to the hand, fixing the elbow at 90° of flexion, while holding the wrist neutral. Movement of the scapula was not restricted. The upper extremity was evaluated in a single posture with the shoulder abducted 90° at the side. This posture was chosen to evoke the greatest contributions from the latissimus dorsi and pectoralis major based on their length and instantaneous moment arms [147,157]. Three-dimensional shoulder joint torques were measured via a six degrees-of-freedom load cell (JR3, Inc., Woodland, California). Only the arm treated for primary breast cancer, the arm treated with unilateral prophylactic mastectomy and reconstruction, or the dominant arm in the case of bilateral prophylactic mastectomy and reconstruction was assessed.

Isometric shoulder strength was measured as participants performed maximum voluntary contractions in the positive and negative directions of three shoulder movement planes: flexion/extension, ad/abduction, and internal/external rotation. The experimental procedures that follow were scaled to the maximum voluntary contractions of each participant. This is common during biomechanical assessments to ensure each participant provide similar effort throughout the experiment.

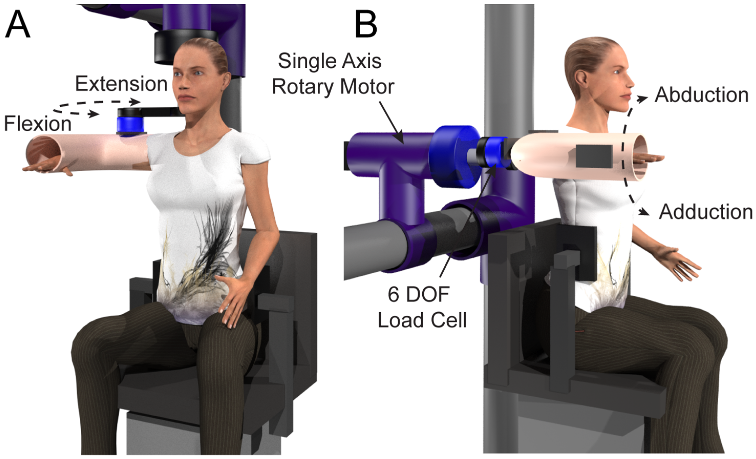

Figure 3.1 Visualization of experimental setup. Participants were seated in a custom-built chair with their affected limb attached to a computer-controlled rotary motor via a plastic, removable cast. A 6 degrees-of-freedom load cell collected shoulder forces and torques. Maximal shoulder strength was obtained in the positive and negative direction of each measurement plane, while shoulder stiffness was collected at rest and during volitional contraction in two measurement planes: the horizontal (A) and vertical (B) planes. Visual feedback was provided via LCD screen in order to ensure torque accuracy.

Robot-assisted measures of shoulder stiffness were used to assess post-operative changes in upper extremity function following mastectomy and breast reconstruction. These methods offer several benefits over traditional clinical assessments, including objective measures of joint stiffness and the ability to assess stiffness during volitional contractions. Our methods for assessing shoulder stiffness have previously been described in greater detail [152,158].

*S*houlder stiffness was examined in two planes of motion: flexion/extension or adduction/abduction (Figure 3.1). In each measurement plane, the motor applied a series of small, stochastic perturbations (0.06 radian amplitude) about the shoulder joint while participants remained at rest (0% MVC), or maintained shoulder torques scaled to ±10% MVC in each plane of motion. Each trial lasted sixty seconds, during which participants utilized visual feedback to assist in maintaining each prescribed torque. Prior to data collection, participants were asked to remain relaxed and were then acclimated to the perturbations with one 60 second trial. Each task (at rest, +10% MVC, -10% MVC) was performed twice in each plane of motion (flexion/extension or adduction/abduction) for a total of 12 trials.

Shoulder joint stiffness was estimated using a validated system identification approach that began by measuring joint impedance, the dynamic relationship between the torque response to a forced change in shoulder posture (perturbations) [94,159]. Joint impedance was represented as a frequency response function parameterized by a 2nd order numerical approximation consisting of inertial (I), viscous (B), and stiffness (K) parameters. This project focuses on the stiffness component, which acts as an objective surrogate measure for clinical assessments of shoulder stability, as our measures of shoulder stiffness require participants to coordinate the co-activations of all shoulder musculature in order to resist perturbation.

Data and Statistical Analyses

Statistical tests were performed using SPSS (v24, IBM Corporation, Chicago, Illinois). Group differences in demographic characteristics (e.g. age, height, weight, etc.) were assessed using one-way ANOVAs, or chi-squared tests when characteristics were represented as frequencies. Post-hoc Bonferroni-corrected pairwise comparisons were utilized when applicable. We tested our hypothesis that objective measures of shoulder function would influence the relationship between breast reconstruction technique and patient-reported outcomes using mediation-based regression analyses (Hayes Model Type 4, PROCESS macro) (Figure 3.2) [160]. Briefly, mediation analysis is an alternative approach to multivariate linear regression that tests a causal chain where a predictor (breast reconstruction technique) influences a mediator variable (functional shoulder biomechanics), which ultimately influences an outcome variable (PROMIS-UE, QuickDASH, SPADI, SF12-PCS, SF12-MCS). In order to determine significance, 95%

confidence intervals for direct and mediated effects were derived from experimental data using bootstrap with replacement repeated 5000 times. Sobel tests assessed the statistical significance of the mediation variables. Patients with DIEP flap reconstructions served as our control group as they had undergone mastectomy and breast reconstruction while avoiding the disinsertion of shoulder musculature. All analyses utilized a significance level of $\alpha = 0.05$. The effect sizes (*Cohens* f^2) for all direct (pathways a_i, b_k, and c') effects were calculated to distinguish between small ($f^2 \geq 0.02$), moderate ($f^2 \geq 0.15$), and large ($f^2 \geq 0.35$) clinically relevant results[161]. The accuracy and utility of effect sizes for indirect effects (pathway $a_i \times b_k$) is questionable, and are therefore not included[162].

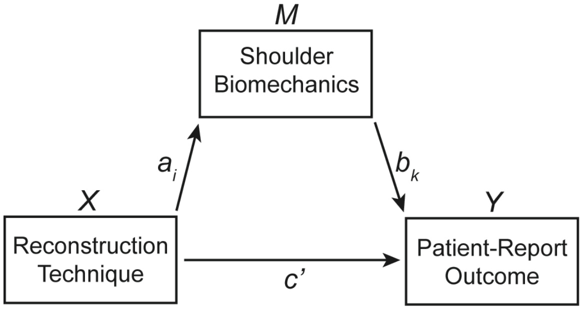

Figure 3.2 Schematic of mediation model (Hayes Model 4) investigating the influence of breast reconstruction technique (X) on patient-reported outcomes (Y), when mediated by measures of functional shoulder biomechanics (M). The a_i pathway describes the direct effect of breast reconstruction technique (i = LD + subpectoral implant, subpectoral implant, DIEP flap) on measures of functional shoulder biomechanics. The b_k pathway describes the direct effect of functional shoulder biomechanics (k = individual measures of shoulder strength, stiffness) on patient-reported outcomes. The c′ pathway describes the direct effect of breast reconstruction technique on patient-reported outcomes when controlling for functional shoulder biomechanics. The influence of shoulder biomechanics as a mediator between breast reconstruction technique and patient-reported outcomes can be determined as the product of the *a* and *b* pathways ($a_i \times b_k$).

3.4 Results

Patient Characteristics

One-hundred and fifty-five women were identified by retrospective chart review. Of those contacted, 46 women consented to participate in a single experimental session and subsequently completed the online surveys. There were no significant differences in any demographic measure between reconstructive groups (all $F<2.82$, $p\geq0.07$) (Table 3.1). The LD + subpectoral implant group was examined an average of 647 days post-operatively, the subpectoral implant group 609 days post-operatively, and the DIEP flap group 750 days post-operatively. More LD + subpectoral implant patients required pre-reconstruction radiation therapy (85.7%) than did DIEP flap (52.9%) or subpectoral implant (6.7%) patients. A small subset of patients with subpectoral implant (6.7%) and DIEP flap (5.9%) reconstruction underwent physical therapy, but no patients with LD + subpectoral implant reconstructions reported physical therapy. Patients that underwent physical therapy did so to address limited range of motion following a period of self-administered rehabilitation exercises.

Table 3.1 Patient Characteristics by Treatment Group. Values represent mean (standard deviation) or relative rates (%). Bolded terms are significant at p < 0.05.

	Latissimus Flap	Subpectoral	DIEP Flap	*p*
n	12	17	17	
Age (years)	53 (10)	49 (10)	51 (8)	0.50
BMI (kg/m^2)	30 (6)	26 (4)	30 (6)	0.07
Days Post Reconstruction	647 (140)	609 (216)	750 (233)	0.07
Former Smoker	1 (7.1%)	2 (13.3%)	1 (5.9%)	0.83
Radiation	12 (85.7%)	1 (6.7%)	9 (52.9%)	**0.00**
Chemo	12 (85.7%)	5 (33.3%)	9 (52.9%)	**0.00**
Comorbidities	11 (78.6%)	10 (66.7%)	8 (47.1%)	**0.04**
Hypertension	2 (14.3%)	3 (20.0%)	2 (11.8%)	0.88
Diabetes	3 (21.4%)	1 (6.7%)	2 (11.8%)	0.32
Hyperlipidemia	4 (28.6%)	3 (20.0%)	2 (11.8%)	0.34

Other Cardiac	0 (0)	4 (26.7%)	0 (0)	**0.02**
Pulmonary	4 (28.6%)	2 (13.3%)	3 (17.7%)	0.34
Mastectomy Indication				
Breast Cancer	12 (100%)	12 (80.0%)	14 (82.4%)	0.12
BRCA1	0	1 (6.7%)	6 (17.6%)	**0.01**
Family Hx/high risk	0	2 (13.3%)	0 (0)	0.17
Previous Malignancy	4 (28.6%)	3 (20.0%)	3 (17.7%)	0.82
Axillary Surgery				
None	0	3 (20.0%)	5 (29.4%)	0.12
SLNB	6 (42.9%)	11 (73.3%)	7 (41.2%)	0.38
ALND	3 (21.4%)	1 (6.7%)	4 (23.5%)	0.29
SLNB+ALND	4 (28.6%)	0	1 (5.9%)	**0.01**
N/A	1 (7.1%)	0	0	
Laterality				
Unilateral	5 (35.7%)	3 (20.0%)	10 (58.8%)	**0.04**
Bilateral	9 (64.3%)	12 (80.0%)	7 (41.2%)	0.11
Timing				
Delayed	8 (57.1%)	1 (6.7%)	5 (29.4%)	**0.00**
Intermediate	5 (35.7%)	14 (93.3%)	11 (23.9%)	0.08
Hybrid	1 (7.1%)	0	1 (5.9%)	0.52

Mediation-Based Regression Analyses between Reconstruction Technique, Functional Shoulder Biomechanics, and Patient-Reported Outcomes

We first examined the direct effect of reconstruction technique on measures of functional shoulder biomechanics (pathway a_i). We found that reconstruction technique predicted maximal shoulder adduction ($R^2=0.23$, $p=0.009$, $f^2=0.30$), abduction ($R^2=0.16$, $p=0.04$, $f^2=0.19$), and internal rotation strength ($R^2=0.12$, $p=0.043$, $f^2=0.14$) (Figure 3.3). An examination of group differences revealed that LD + subpectoral implant patients were 29% weaker in adduction strength than subpectoral implant patients ($\beta=-10.9$, $SE=5.1$, $p=0.04$). When compared to DIEP flap patients, LD + subpectoral implant patients were 38% weaker in adduction ($\beta=-16.4$, $SE=5.0$, $p=0.003$), 34% weaker in abduction ($\beta=-14.7$, $SE=5.6$, $p=0.01$), and 29% weaker in internal rotation (*β=-6.7, SE=3.2, p=0.04*) strength. We also found that the reconstruction technique utilized predicted shoulder stiffness while maintaining adduction torques ($R^2=0.23$, *p=0.04*) (Figure 3.4). In this case, LD + subpectoral implant patients exhibited 35% less stiffness than DIEP flap patients did (*β=-18.8, SE=7.3, p=0.014*). Collectively, these results indicate that LD + subpectoral implant patients experience shoulder functional deficits at disproportionately higher rates when compared to subpectoral implant and DIEP flap reconstruction patients.

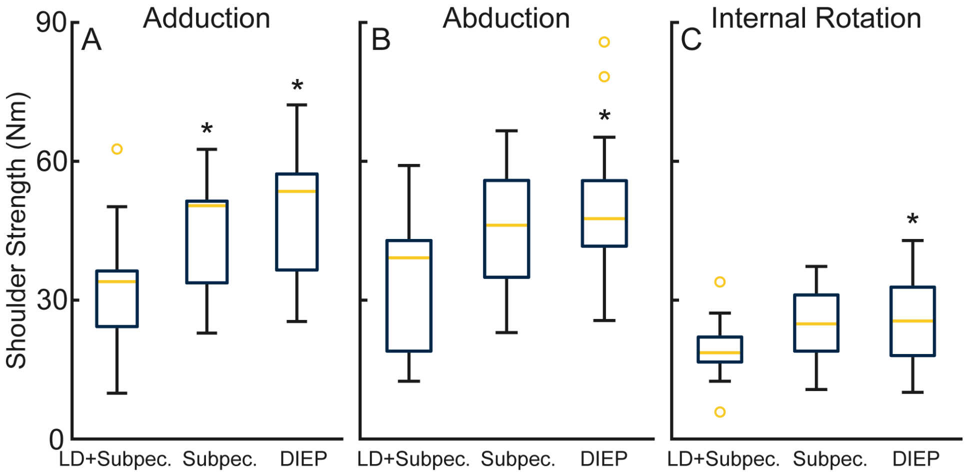

Figure 3.3 Boxplots (group means, 25% quartile, and 75% quartile) representing group differences in maximal shoulder strength. Participants performed maximal voluntary contractions in the positive and negative directions of each measurement plane. Only adduction (A), abduction (B), and internal rotation (C) strength results are shown, as they differed significantly between groups. Outliers are represented by unfilled yellow circles. * Denotes significant difference from LD + subpectoral implant group.

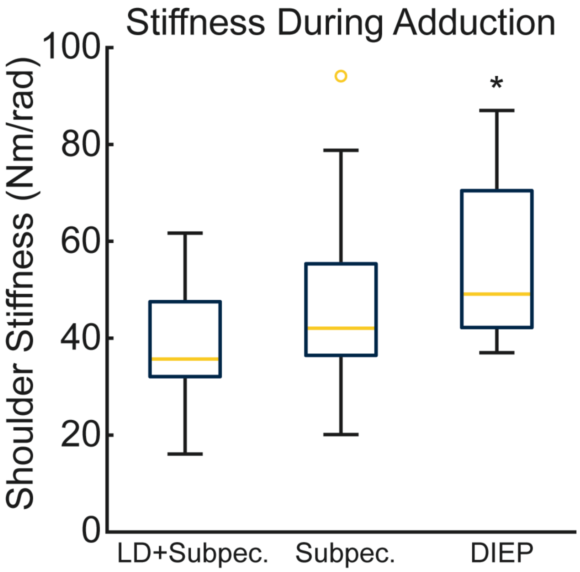

Figure 3.4 Boxplot (group means, 25% quartile and 75% quartile) representing group differences in shoulder stiffness during the maintenance of adduction torques. Participants remained relaxed or maintained volitional shoulder torques scaled to ±10% MVC in each measurement plane while a computer-controlled rotary motor perturbed their shoulder approximately 3 degrees. Outliers are represented by unfilled yellow circles. * Denotes significant difference from LD + subpectoral implant group.

Next, we examined the direct effect of functional shoulder biomechanics on PRO scores (pathway b_i). We found that only a single measure of shoulder strength predicted any PROs (all others: $p>0.055$). Increasing maximal external rotation strength was significantly correlated with increasing PROMIS-UE score ($R^2=0.151$, $\beta=0.3$, $SE=0.1$, $p=0.04$, $f^2=0.18$), indicative of improved patient-reported upper extremity function and reduced pain (Figure 3.5).

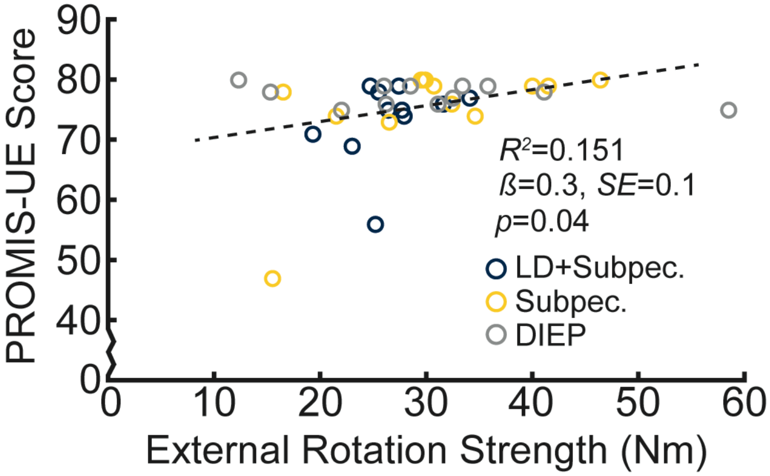

Figure 3.5 Scatterplot representing the relationship between maximal shoulder external rotation strength and scores from the Patient Reported Outcomes Measurement and Information System Upper Extremity Instrument (PROMIS-UE). External rotation strength was able to account for approximately 15% of the variance in the PROMIS-UE score. Increasing external rotation strength was predictive of improving upper extremity function.

We observed that measures of shoulder stiffness were overall better predictors of PROs than shoulder strength when controlling for breast reconstruction technique. Increasing shoulder stiffness at rest in the vertical plane was associated with increasing QuickDASH ($R^2=0.133, \beta=0.5, SE=0.2, p=0.03, f^2=0.15$) score and decreasing SF12-MCS ($R^2=0.199, \beta=-0.5, SE=0.2, p=0.02, f^2=0.25$) scores (Figures 3.6 and 3.7), indicative of worsening in both patient-reported upper extremity function and psychosocial well-being. Increasing shoulder stiffness at rest in the horizontal plane ($R^2=0.169, \beta=-0.9, SE=0.4, p=0.02, f^2=0.20$), and during the maintenance of flexion ($R^2=0.169, \beta=-0.2, SE=0.08, p=0.02, f^2=0.20$) and extension torques ($R^2=0.229, \beta=-0.3, SE=0.09, p=0.01, f^2=0.30$) were all associated with decreasing SF12-MCS score when controlling for breast reconstruction technique, also indicative of worsened patient-reported psychosocial well-being (Figure 3.7).

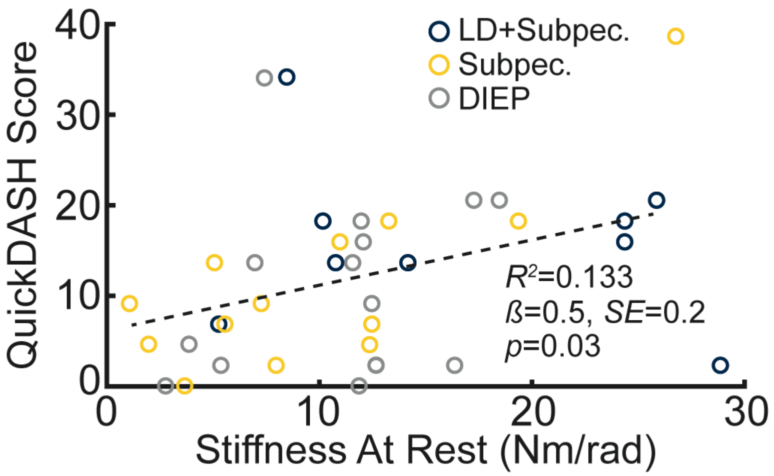

Figure 3.6 Scatterplot representing the relationship between shoulder stiffness at rest in the vertical plane and scores from the abbreviated version of the Disabilities of the Arm, Shoulder and Hand Score (QuickDASH). Shoulder stiffness at rest in the vertical plane accounted for approximately 13% of the variance in the QuickDASH score and increasing stiffness was predictive of worsening upper extremity function.

The direct effect of breast reconstruction technique on PROs was assessed via the *c′* pathway of our mediation analyses (Supplemental Table A.1). We found that, when controlling for functional shoulder biomechanics, the breast reconstruction technique utilized did not directly predict any patient-reported outcome measure (*all* $p \geq 0.08$).

Regression-based mediation analyses were used to investigate functional shoulder biomechanics as a mediator between breast reconstruction technique on patient-reported measures of physical and psychosocial well-being (pathway $a_i \times b_k$) (Supplemental Table A.2). We found that the breast reconstruction technique utilized did not indirectly predict any PROs, regardless of which measure of functional shoulder biomechanics was acting as mediator (all $p \geq 0.24$).

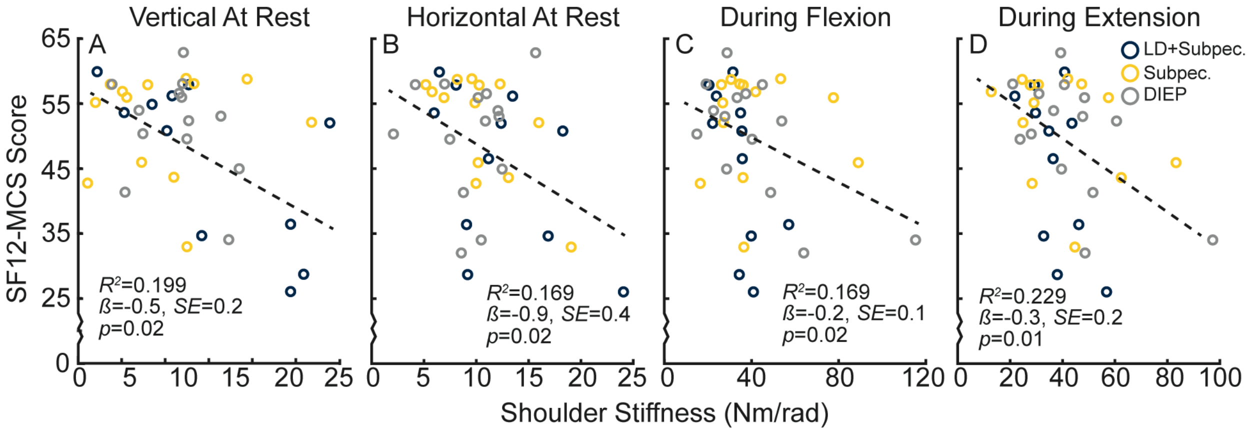

Figure 3.7 Scatterplots representing the relationships between shoulder stiffness at rest in the vertical (A) and horizontal plane (B), and while maintaining flexion (C) and extension (D) torques and scores from the 12-item Short Form Survey Mental Composite Score (SF12-MCS). All four measures of shoulder stiffness exhibited a significant negative relationship with SF12-MCS score, indicating worsened psychosocial well-being with increasing stiffness at rest and during volitional contraction in the horizontal plane.

3.5 Discussion

This study investigated the role of objective, robot-assisted measures of shoulder biomechanics as mediators of the relationship between post-mastectomy breast reconstruction technique and patient-reported physical and psychosocial well-being. We report that none of the included functional shoulder biomechanics served as mediators in the relationship between breast reconstruction technique and patient-reported functional and psychosocial well-being. However, we found that multiple measures of functional shoulder biomechanics were predictive of patient-reported outcomes. Shoulder strength was predictive of patient-reported physical function, whereas shoulder stiffness predicted both physical and psychosocial well-being. Finally, we found that the breast reconstruction technique utilized predicted several measures of shoulder strength and stiffness, with LD + subpectoral implant patients exhibiting significantly reduced shoulder strength when compared to subpectoral implant patients and significantly reduced strength and stiffness when compared to DIEP flap patients. These findings suggest that the breast reconstruction technique used will uniquely influence functional shoulder biomechanics and that multiple measures of shoulder biomechanics can capture self-reported physical and psychosocial well-being. However, it appears that the functional shoulder biomechanics measured in the current study does not mediate the effect of breast reconstruction technique on patient-reported outcomes. Nevertheless, our results emphasize the need to properly manage shoulder function after mastectomy and breast reconstruction in order to ensure adequate patient quality of life.

The assessment of a patient's upper extremity range of motion or strength following breast reconstruction is frequently performed in a clinical setting by comparing the compromised and uncompromised sides. These evaluations are clinically convenient but do not provide an accurate measure of a patient's ability to initiate movement and maintain postural control during functional tasks. Additionally, the repeatability of clinical assessments of shoulder function is questionable [89,163]. Our study utilized novel, objective, robot-assisted measurements of shoulder strength and stiffness to assess post-operative changes in functional shoulder biomechanics following three common breast reconstruction techniques. Our findings that LD + subpectoral implant patients exhibit significantly lower shoulder strength than subpectoral implant patients and significantly lower strength and stiffness when compared to DIEP flap patients is in line with previous findings from both objective and subjective measures of shoulder strength and stiffness [68,76,79,134,141,158]. Interestingly, no significant differences existed between the subpectoral implant and DIEP flap participants in shoulder strength or stiffness, despite the disinsertion of a portion of the pectoralis major required to complete a subpectoral implant breast reconstruction. Although the LD + subpectoral implant patients included in the current cohort underwent the combined disinsertion of both the pectoralis major and latissimus dorsi, these results for the subpectoral implant patients indicate the likelihood that the observed strength and stiffness deficits in the LD + subpectoral implant group are due solely to the disinsertion of the latissimus dorsi.

We utilized five validated PRO instruments to probe the clinical impact of our functional shoulder biomechanics findings. Shoulder strength is often used clinically as a barometer for a patient's upper extremity functional capacity. Our results suggest that shoulder stiffness, which examines a patient's resistance to movement, provides more insight into a patient's ability to interact with their daily environment than shoulder strength alone. Specifically, we found that only a single measure of shoulder strength was predictive of patient-reported physical well-being, whereas multiple measures of shoulder stiffness were predictive of upper extremity function and/or general psychosocial well-being. Common breast reconstruction techniques result in reduced shoulder stiffness [152,158]. This study is the first to show that reduced shoulder stiffness is connected to improved patient-reported physical and psychosocial well-being. It has been suggested that an overly stiff joint may negatively impact the quality of life, such as in the case of adhesive capsulitis, which may affect up to 18% of breast cancer patients [164,165]. No participants in this study had a previous diagnosis of adhesive capsulitis given our exclusion criteria, but future work is needed to relate changes in shoulder stiffness and quality of life measures in breast cancer patients with the onset of adhesive capsulitis.

We performed a novel analysis of the role of functional shoulder biomechanics as mediators in the relationship between breast reconstruction technique and patient-reported physical and psychosocial quality of life. We found that no measure of functional shoulder biomechanics mediated the relationship between breast reconstruction technique and patient-reported functional and psychosocial measures. These findings may simply reflect that the specific measures of shoulder biomechanics influenced by breast reconstruction techniques were not the same biomechanical measures that were predictive of patient-reported outcomes. For example, breast reconstruction technique affected shoulder adduction, abduction, and internal rotation strength, and shoulder stiffness while maintaining adduction torques, whereas external rotation strength and stiffness at rest in the vertical and horizontal planes and during the maintenance of flexion and extension torques were predictive of several patient-reported outcomes scores. While we thoroughly and objectively assessed functional shoulder biomechanics in the current study, it is possible that other biomechanical measures not assessed here may serve as mediators between breast reconstruction technique and patient-reported outcomes. These results should not undermine our key findings that 1) breast reconstruction technique uniquely influences shoulder biomechanics, and 2) multiple measures of shoulder biomechanics can capture both physical and psychosocial quality of life changes. Regardless of the breast reconstruction technique used, the optimal delivery of reconstruction care moving forward should focus in part on restoring shoulder function, including minimizing the loss of shoulder strength and managing shoulder stiffness.

This study has limitations. The cross-sectional design did not allow for longitudinal patient analysis, obtaining both pre- and post-reconstruction biomechanical and PRO data. We attempted to mitigate this weakness by only recruiting participants from well-defined groups that possessed minimal covariates. Issues regarding aesthetics and satisfaction may influence PROs; however, by utilizing function-based PRO surveys we aimed to avoid those confounding elements inherent to all breast reconstruction outcomes research. The patient populations utilized in the current study were not homogenous with regard to radiotherapy and axillary surgery. While radiotherapy and axillary surgery may cause pain, shoulder range of motion deficits, and lymphedema in a subset of patients, the inclusion of radiotherapy and axillary surgery has not been shown to influence shoulder biomechanics [40,112-115,166,167]. Our functional shoulder biomechanics were obtained in a single posture, which was chosen in order to maximize the contributions from the pectoralis major and latissimus dorsi muscles. Additional postures encompassing the vast range of motion of the shoulder would provide greater insight into patient function and may more accurately represent shoulder posture during activities of daily living. Finally, we were unable to control for the extent of pectoralis major muscle disinsertion. Although we attempted to maintain consistency by assessing patients from a single surgeon, it is possible that the volume of pectoralis muscle disinserted varied between patients.

3.6 Conclusions

In this cohort of women who underwent post-mastectomy breast reconstruction, LD + subpectoral implant breast reconstructions resulted in significant shoulder strength and stiffness deficits when compared to subpectoral implant and DIEP flap reconstructions. Furthermore, shoulder stiffness and to a lesser extent shoulder strength predicted patient-reported physical and psychosocial well-being. These results suggest greater emphasis should be placed on the peri-operative screening and managing breast cancer patients undergoing breast reconstruction for deficits in both shoulder strength and stiffness to optimize their quality of life.

Chapter 4. The Functional Integrity of the Shoulder Joint and Pectoralis Major Following Subpectoral Implant Breast Reconstruction

The following chapter was published in the *Journal of Orthopaedic Research,* and all images contained in this chapter are copyrighted by Wiley. Please refer to the following publication when referencing this work: Leonardis JM, Lyons DA, Giladi AM, Momoh AO, Lipps DB. Functional Integrity of the Shoulder Joint and Pectoralis Major Following Subpectoral Implant Breast Reconstruction. Journal of Orthopaedic Research. 2019;37(7):1610-19.

4.1 Abstract

Subpectoral implants for breast reconstruction after mastectomy requires the surgical disinsertion of the sternocostal fiber region of the pectoralis major. This technique is associated with significant shoulder strength and range of motion deficits, but it is unknown how it affects the underlying integrity of the shoulder joint or pectoralis major. The aim of this study was to characterize the long-term effects of this reconstruction approach on shoulder joint stiffness and pectoralis major material properties. Robot-assisted measures of shoulder strength and stiffness and ultrasound shear wave elastography images from the pectoralis major were acquired from 14 women an average of 549 days (range: 313-795 days) post reconstruction and 14 healthy, age-matched controls. Subpectoral implant patients were significantly weaker in shoulder adduction ($p < 0.001$) and exhibited lower shoulder stiffness when producing submaximal adduction torques ($p = 0.004$). The underlying material properties of the clavicular fiber region of the pectoralis major were altered in subpectoral implant patients, with significantly reduced shear wave velocities in the clavicular fiber region of the pectoralis major when generating adduction torques ($p = 0.023$). The clinical significance of these findings are that subpectoral implant patients do not fully recover

shoulder strength or stability in the long-term, despite significant recovery time and substantial shoulder musculature left intact. The impact of these procedures extends to the remaining, intact volume of the pectoralis major. Optimization of shoulder function should be a key aspect of the post-reconstruction standard of care.

4.2 Introduction

A growing number of women diagnosed with breast cancer will have the disease managed with mastectomy, a surgical procedure that removes all breast tissue. Increasing mastectomy rates have led to a growing number of post-mastectomy breast reconstruction surgeries, with approximately 107,000 such procedures performed annually in the United States[14,27-29,168]. Post-mastectomy breast reconstructions are a group of surgical procedures that restore the look and feel of natural breast tissue by utilizing either autologous tissue or an artificial implant. Traditional two-stage subpectoral implant-based breast reconstructions (subpectoral implant) account for nearly 60% of all post-mastectomy breast reconstructions[16,27]. The first stage of this approach requires the disinsertion of the sternocostal fibers of the pectoralis major (PM) from its attachments on the costal cartilage and lower sternum to allow placement of a tissue expander beneath the muscle. The volume of this expander is increased over several months, thereby stretching the PM to accommodate an implant of the desired size. The second surgical stage is a less extensive procedure whereby the temporary tissue expander is exchanged for a permanent implant.

Disinserting the sternocostal fiber region of the PM can lead to significant long-term functional deficits for patients undergoing post-mastectomy breast reconstruction. The intact PM contributes to shoulder adduction, flexion, and internal rotation[147,157], and as such, its disinsertion results in significant shoulder strength deficits[82]. Adequate PM function is also required for the maintenance of healthy shoulder stability[92,169,170]. Traditionally, shoulder stability is measured during a clinical assessment by comparing the resistance provided by affected and unaffected shoulders when passively moved through a range of motion. Unfortunately, the subjectivity of clinical assessments of shoulder stability raises concerns regarding their accuracy and repeatability[88-90].

Shoulder stiffness is a biomechanical measure of the resistance of the shoulder to movement, which is key for the execution of activities of daily living[94,95,97-99]. Biomechanical measures of shoulder stiffness provide quantitative insights into the net contributions of all soft tissues that stabilize the shoulder. A shoulder with reduced stiffness could be more prone to instability due to less resistance to movement, while a shoulder with enhanced stiffness is resistant to movement and could be prone to disorders like adhesive capsulitis. However, this objective measure cannot differentiate between the contributions of individual soft tissues. Ultrasound shear wave elastography (SWE) can non-invasively estimate the material properties of individual soft tissues *in vivo* in both healthy and clinical populations[104,106-109,171-173]. When collected at rest and during active contraction, shear wave velocity (SWV) provides information regarding the contributions of individual musculature[105]. In combination with objective measures of shoulder stiffness, shear wave elastography provides valuable insight into how subpectoral implant breast reconstruction influences the material properties of the PM.

The primary objective of this study was to determine the effect of subpectoral implant breast reconstruction on the functional integrity of the shoulder joint using objective and reliable robot-assisted measures of shoulder joint strength and stiffness. The secondary objective of this study was to examine how subpectoral implant breast reconstruction influences the material properties of the sternocostal and clavicular fiber regions of the PM at rest and during active contraction. Finally, we assessed the clinical significance of our shoulder strength and stiffness and pectoralis major material properties findings. To achieve these objectives, we acquired robot-assisted biomechanical measures of multidimensional shoulder strength and stiffness, ultrasound SWE-based measures of PM shear wave velocities, and patient-reported outcomes surveys from subpectoral implant breast reconstruction patients and healthy, age-matched controls. We hypothesized that, when compared to healthy controls, subpectoral implant breast reconstruction patients would exhibit significantly reduced strength in shoulder adduction, flexion, and internal rotation, and significantly reduced shoulder stiffness while producing vertical adduction torques. We further hypothesized that this reduced shoulder strength and stiffness would be driven by underutilization of the PM, which would be evidenced by altered PM material properties. Finally, we hypothesized that reduced shoulder strength and stiffness, and underutilization of the PM would be associated with poorer self-reported upper extremity function.

4.3 Methods

Participants

This was a retrospective cohort study (level of evidence: 3) that investigated the long-term effects of subpectoral implant breast reconstruction on shoulder stiffness and the material properties of the pectoralis major. Twenty-eight women participated in one experimental session each (Table 4.1). A retrospective chart review from a single surgeon's practice at the University of Michigan was performed to identify women who had previously undergone breast reconstruction between 2014 and 2017. Patients were excluded if they had previously experienced any neuromuscular or orthopaedic disorders affecting the upper limb. Fourteen eligible patients elected to participate. All breast reconstruction patients underwent a two-stage subpectoral implant procedure that required the disinsertion of the sternocostal fiber region of the PM. Fourteen healthy, age-matched women were also recruited from the University of Michigan and Ann Arbor communities. Participants were provided with written consent to procedures approved by the University of Michigan's Institutional Review Board (HUM00114801 and HUM00111519).

Experimental Setup

In a single visit, participants were secured to a Biodex chair (Biodex Medical Systems, Shirley, New York) with movement restricted using chest and waist straps and cushioned plates positioned along the lower back and sides of their torso. A padded, plastic cast extending from the shoulder to the hand attached the participant's examined shoulder to a computer-controlled brushless servomotor (Baldor Electric Company, Fort Smith, AR) (Figure 4.1). The affected arm was examined in the subpectoral implant group, which was the dominant limb in 10 of 14 patients. The affected limb was defined as the limb treated for primary breast cancer, or in the case of bilateral breast cancer, the dominant limb was examined. Only the dominant limb was examined in the 14 healthy controls. Within the cast the elbow was fixed at 90°, the wrist was held neutral, and movement of the scapula was unrestricted. The motor's axis of rotation was aligned with the center of rotation of the glenohumeral joint. Shoulder joint torques were measured using a 6DOF load cell (JR3, Inc., Woodland, CA) attached between the motor crank arm and the cast. Our measurement coordinate system utilized established biomechanical standards[138].

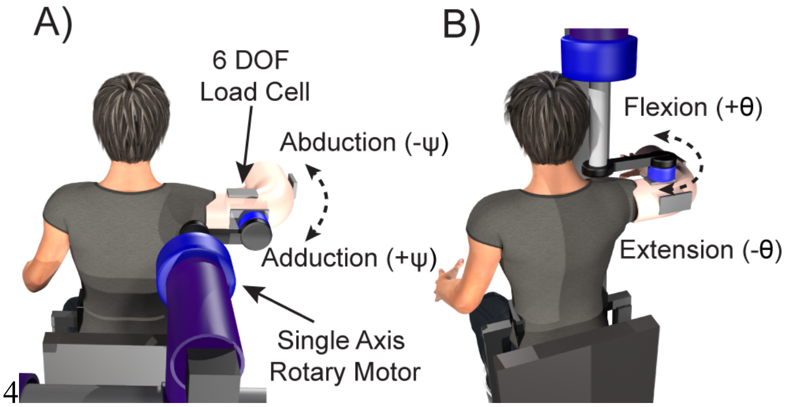

Figure 4.1 Schematic of experimental setup. A single-axis rotary motor perturbed a participant's examined shoulder in one plane of motion while a six-degree-of-freedom load cell measured resultant torques in all three dimensions. Visual feedback was provided via LCD screen. (A) The rotary motor was positioned to move the arm in the vertical plane while participants were relaxed or generating shoulder torques in ± elevation. (B) The rotary motor was positioned to move the arm in the horizontal plane while participants were relaxed or generating shoulder torques in ± plane of elevation.

Experimental Protocol

Participants performed maximal voluntary contractions (MVC) in the positive and negative directions of plane of elevation (θ), rotation (ϕ), and elevation (Ψ). Values obtained from these contractions were used to normalize the remaining trials to each participant's strength. Participants were then examined in elevation and plane of elevation in a random order. Shoulder posture remained constant (shoulder elevated 90°, flexed 0°) across all trials.

Shoulder joint stiffness was measured in each plane by measuring the resultant shoulder torque. In each measurement plane, the motor applied a series of stochastic perturbations presented as a pseudo-random binary sequence with a 0.06 radian amplitude and 150 millisecond switching interval. These perturbation characteristics were chosen to limit the nonlinearity of muscles, while being able to differentiate between joint dynamics and noise due to muscular activity. Perturbation trials lasted for 60 seconds, during which participants were asked to remain relaxed (0% MVC) or to maintain a constant torque scaled to ±10% MVC in the given measurement plane. Visual feedback was provided in order to assist in the maintenance of the prescribed torque. One trial where the participants remained relaxed was included at the beginning of each configuration to acclimate the participants to the sensation of being perturbed. We repeated each perturbation testing condition for six total trials per measurement plane resulting in 14 perturbation trials.

Following shoulder stiffness trials, an Aixplorer ultrasound elastography machine (Supersonic Imagine, Aix en Provence, France) connected to a SL15-4 linear transducer array (Optimization: Standard, Persistance: Medium, Smoothing: 5, Frame Rate: 12 Hz) was used to perform ultrasound SWE on the PM fiber regions while participants remained relaxed (0% MVC) or maintained a constant torque scaled to 10% MVC in adduction or flexion.

When imaging the clavicular fiber region, the probe was initially placed approximately 1 cm inferior to the clavicle over the midpoint of the muscle. The midpoint of the clavicular fiber region was as identified by the midpoint of a line extending from the sternoclavicular joint to the point on the humerus deep to the anterior deltoid. The probe was then slowly shifted inferiorly from the clavicle until it was located mid-belly. Probe location was established similarly for the sternocostal fiber region. When imaging the sternocostal fiber region, the probe was initially placed approximately 4 cm inferior to the sternoclavicular joint over the midpoint of the muscle. The probe was then slowly shifted inferiorly from the sternoclavicular joint until it was located mid-belly. The midpoint of the sternocostal fiber region was initially established as the midpoint of a line extending from the xiphoid process to the point on the humerus deep to the anterior deltoid. This midpoint was then adjusted for each participant by shifting the origin of the line superiorly from the xiphoid process based on individual participant’s anatomy. The orientation of the transducer was considered satisfactory when individual muscle fascicles could be identified on the B-mode ultrasound image. Each B-mode image was superimposed with an elastography color map (2.5 cm x 1 cm) positioned within the belly of the fiber region of interest. The color map provides calculations of SWV for each pixel. The color map size was constant between participants, but its depth relative to the surface of the skin was adjusted depending on individual anatomy. All images were collected by the same experimenter. The order of all of the trials was randomized. Two images were collected for each fiber region, torque task, and motor configuration, resulting in 24 images per participant.

The breast reconstruction patients also completed the Shoulder Pain and Disability Index (SPADI), which is a 13-item patient-reported outcomes survey that provides insight into the level of shoulder pain and disability experienced by the participant during the execution of activities of daily living in the previous seven days [174].

Data Analysis

Shoulder stiffness was first estimated using a single-input, single-output nonparametric system identification[94-96]. Impedance was calculated by relating perturbations in direction *i* to the resultant torque response in the same direction. Stiffness was quantified as the frequency response function H_i between 0 – 10 Hz. This was performed as participants produced torques in one of two different directions: plane of elevation (1) and elevation (2). Nonparametric fits were assessed using variance accounted for (VAF), while partial coherence estimates revealed the frequency ranges where nonparametric fits approximated data well.

$$TQ_\theta(f) = H_\theta(f)\theta(f) \qquad (1)$$

$$TQ_\psi(f) = H_\psi(f)\psi(f) \qquad (2)$$

Frequency response functions were parameterized using a 2nd order linear model consisting of inertial (*I)*, viscous (*B)*, and stiffness (*K)* components (3). These parameters were estimated by substituting $s = i2\pi f$ and fitting a frequency response function with Nelder-Mead non-linear optimization. Only the stiffness component in the specific direction of perturbation (elevation: K_θ, plane of elevation: K_Ψ) is reported, as this is the most clinically relevant parameter for assessing shoulder joint stability.

$$H_i(s) = I_i s^2 + B_i s + K_i(s) \quad (3)$$

Shear wave elastography images were analyzed using a custom MATLAB algorithm (Mathworks Inc, Natick, MA, USA) to systematically quantify fiber regions SWVs[172,173]. This approach began by extracting the SWVs and quality maps for each image. Next, a region of interest within the shear wave color map that corresponded to the muscle alone was manually selected. This ensured that the aponeurosis or other tissues did not bias the data. Depending on individual anatomy, the size of this region of interest differed slightly image to image. The quality map determined the accuracy of our SWV measures pixel by pixel within the region of interest. The quality map reflects the manufacturer's calculation regarding the cross-correlation of shear waves propagating within the tissue. Finally, the algorithm computed the mean SWV for each image from the pixels that possessed a quality map above the 0.7 threshold. The mean SWVs obtained from the two images collected for each fiber region, torque task, and motor configuration are reported.

An external trigger was utilized to obtain an elastography image and collect a two second buffer of torque data (one second prior to and one second after the trigger). Torque data were analyzed in MATLAB, where they were low-pass filtered at 500 Hz with a 6th-order analog Bessel filter and averaged across each 2-s trial. The torque data were then normalized as a percentage of the maximum torque produced for each specific experimental motor configuration.

Statistical Analysis

All statistical procedures were performed in SPSS (v24, IBM Corporation, Chicago, IL, USA). Differences in demographic measures (age, height, mass, BMI) between our experimental groups were investigated using t-tests. We tested our first hypothesis that subpectoral implant patients would exhibit significantly reduced shoulder strength. Using independent t-tests we evaluated the maximum isometric voluntary strength between patients and controls in six separate directions. Significance was set at an adjusted p-value of 0.0083 for these six comparisons using Bonferroni correction. We tested our hypothesis that subpectoral implant patients would exhibit significantly reduced shoulder stiffness using a separate two-way ANOVA for stiffnesses in each measurement plane (elevation, plane of elevation). Our outcome measure was stiffness, while torque task (at rest, ± elevation, and ± plane of elevation) and experimental group (subpectoral implant and healthy control) were fixed factors. We tested our hypothesis that subpectoral implant patients would exhibit altered pectoralis major material properties using a three-way ANOVA, where SWV was the outcome measure and fiber region (clavicular, sternocostal), torque task (rest, flexion, adduction), and experimental group were fixed factors. Bonferroni corrections for multiple comparisons were used for post hoc analyses. We tested our hypothesis that reduced shoulder strength and stiffness, and underutilization of the pectoralis major would be associated with poorer patient-reported outcomes using a forced-entry regression analysis where SPADI score was the dependent variable and measures of shoulder strength and stiffness, and PM material properties were independent variables. ANOVAs and regression analyses utilized a significance level of $p<0.05$. Observed power is reported for all significant findings.

4.4 Results

Demographics

No significant differences in age ($t_{26} = -1.136, p = 0.27$), height ($t_{26} = -0.265, p = 0.79$), weight ($t_{26} = 1.325, p = 0.20$), or BMI ($t_{26} = 1.805, p = 0.09$) existed between the experimental groups (Table 4.1). The subpectoral implant reconstruction patients were evaluated an average (SD) of 549 (39) days post-operatively.

Table 4.1 Mean (standard error) participant demographics for each experimental group. Group differences were explored using t-tests. * denotes a significant difference at $p < 0.05$.

	Subpectoral	Healthy Control	*p*
Number of Participants	14	14	
Age (yrs)	49 (2.6)	53 (1.3)	0.27
Height (m)	1.64 (.01)	1.64 (.02)	0.79
Weight (kg)	71 (3.4)	65 (3.0)	0.20
BMI (kg/m^2)	26 (1.3)	24 (0.71)	0.09
Days Post-Operative	549 (39)		
Dominant/Non-Dominant Limb	10/4		
Radiation Therapy (Yes/No)	0/14		
Chemotherapy (Yes/No)	5/9		
Axillary Lymph Node Dissection (Yes/No)	0/14		
Sentinel Lymph Node Dissection (Yes/No)	12/14		

Multidimensional Shoulder Strength and Stiffness

The subpectoral implant group was significantly weaker in adduction than controls ($t_{26} = -3.765, p = 0.001, power = 0.943$) (Figure 4.2). The subpectoral implant patients were also weaker in internal rotation ($t_{26} = -2.105, p = 0.045$), but this did not reach statistical significance after controlling for multiple strength comparisons. There were no significant differences between groups when producing maximal abduction ($t_{26} = -0.930, p = 0.361$), flexion ($t_{26} = -0.898, p = 0.377$), extension ($t_{26} = -0.108, p = 0.915$), or external rotation ($t_{26} = -1.428, p = 0.165$) torques.

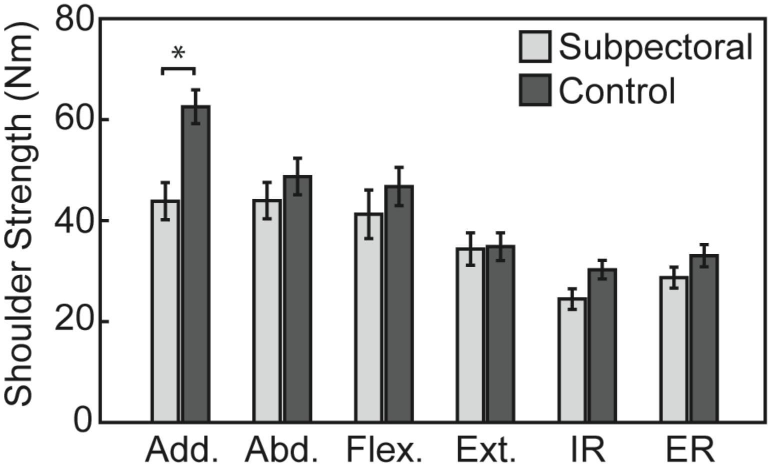

Figure 4.2 Participants performed maximal isometric shoulder torques in the positive and negative directions in the elevation (adduction, abduction), plane of elevation (flexion, extension), and rotation planes (internal rotation, external rotation). Bars represent mean ± standard error isometric shoulder strength (Nm) error for each experimental group. * denotes significant difference at $p < 0.05$.

Shoulder Stiffness

System identification of shoulder joint stiffness allowed us to uncover inherent differences in the mechanical integrity of the shoulder between subpectoral implant patients and healthy controls. Figure 4.3 shows frequency response functions and 2nd order linear model fits for representative subpectoral implant and control participants. Stiffness is represented by the model fit as it approaches 0 Hz. The representative participant from each experimental group exhibited similar shoulder stiffness while at rest (Figure 4.3A) as evidenced by similar model fits between 0-10 Hz. As the participants produced volitional shoulder adduction torque (Figure 4.3B), the healthy participants exhibited noticeably greater shoulder stiffness when compared to the subpectoral implant patients. Overall, these system identification methods were robust, as the model fits were able to account for 87 ± 9% of all variance in experimental torque across all subjects and stiffness trials.

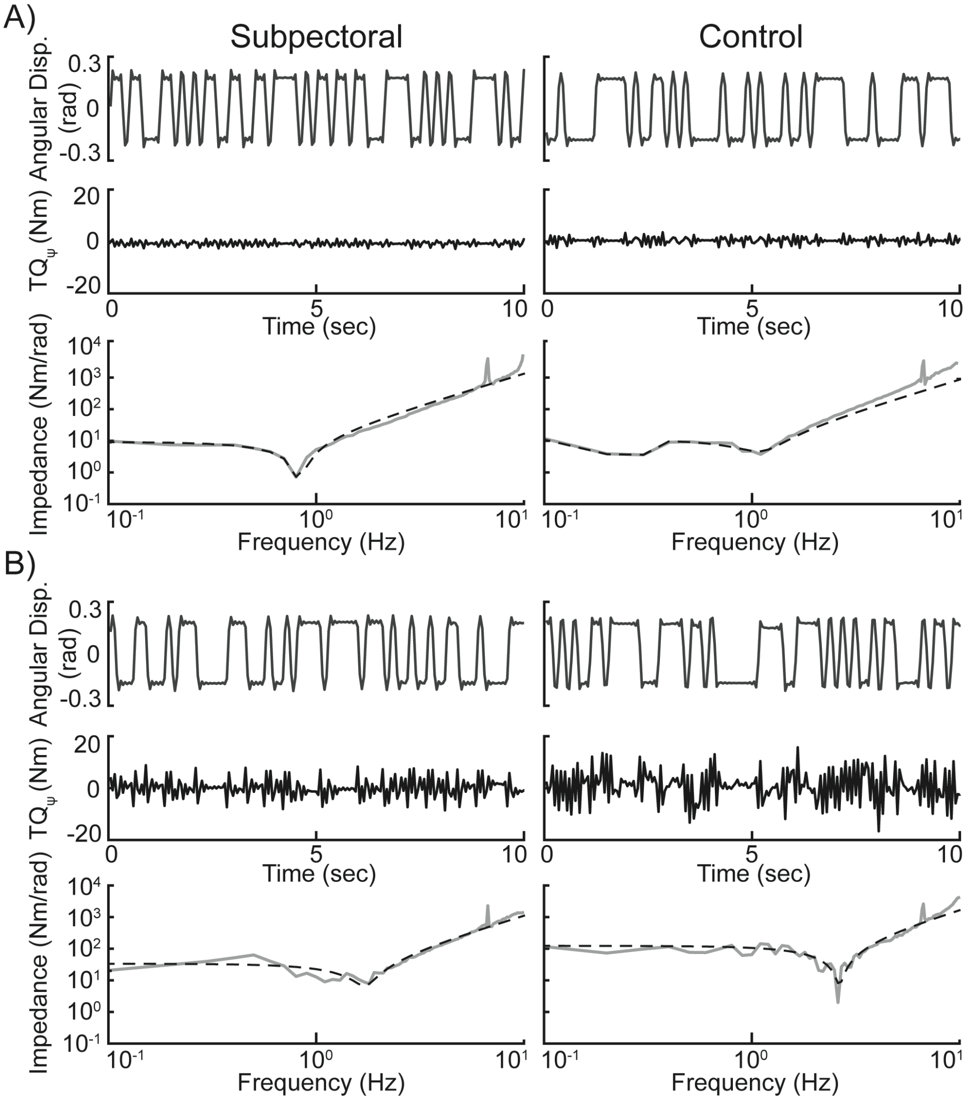

Figure 4.3 Representative frequency response functions (Light Gray) relating the torque response (Black) to a 1-D perturbation (Dark Gray). Figure 4.3A presents data from one participant from each experimental group while those participants remained relaxed. Figure 4.3B presents data when those same participants produced volitional shoulder torque scaled to +10% MVC adduction. Participants were perturbed for 60 seconds total, but only 10 seconds of data are shown. A 2nd order approximation to the frequency response functions is represented as dashed black lines. Stiffness is represented by the model fit between 0-10 Hz.

There was a main effect of experimental group on shoulder stiffness when participants were perturbed in elevation, with the subpectoral group exhibiting significantly reduced shoulder stiffness ($F_{1,1} = 9.005, p = 0.004, power = 0.842$). There was also a main effect of task on shoulder stiffness in elevation ($F_{1,2} = 47.769, p < 0.001, power = 1$). Specifically, stiffnesses during adduction and abduction were similar to one another ($p = 0.798$), but both were significantly greater than stiffness at rest (adduction: $p < 0.001$, flexion: $p < 0.001$). Multiple comparisons showed that the subpectoral implant group exhibited 45.1% lower shoulder stiffness when compared to healthy controls while generating vertical adduction torques ($p = 0.001$) (Figure 4.4). Multiple comparisons also revealed a difference between the groups when producing abduction torques, but did not reach statistical significance ($p = 0.09$).

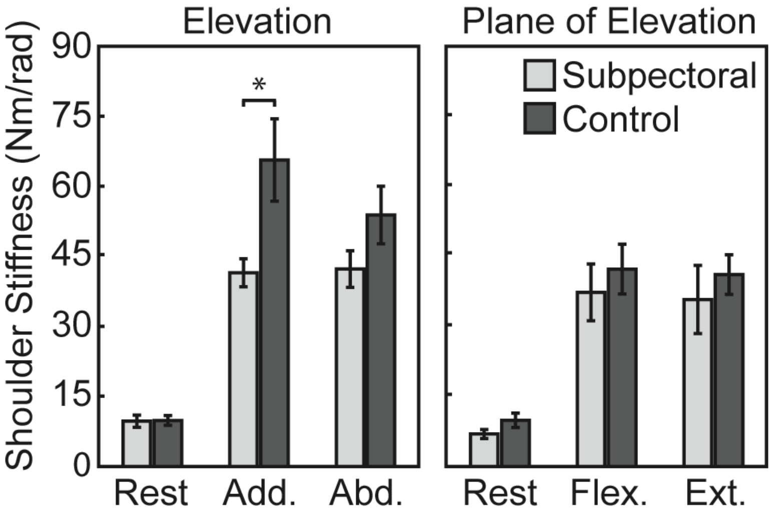

Figure 4.4 Participants were perturbed in elevation (A) and plane of elevation (B). During perturbation trials, participants were asked to remain relaxed (Rest) or to maintain torques scaled to -10% MVC (Adduction/Flexion) and +10% MVC (Abduction/Extension) in each plane of motion. Bars represent mean ± standard error shoulder stiffness (Nm/rad) for each experimental group. * denotes significant difference at $p < 0.05$.

When participants were perturbed in the plane of elevation, there was a main effect of task ($F_{1,2} = 27.040, p < 0.001, power = 1$), but not group ($F_{1,1} = 1.257, p = 0.266$). Similar to findings from elevation, shoulder stiffness during flexion and extension were similar to one another ($p =$

1.000), but both were significantly greater than stiffness at rest (adduction: $p < 0.001$, flexion: $p < 0.001$).

Pectoralis Major Fiber Region Material Properties

There was a main effect of experimental group ($F_{1,1} = 6.257, p = 0.013, power = 0.701$) on SWVs, with the healthy group exhibiting significantly greater SWVs than the subpectoral implant group. There was also a main effect of task ($F_{1, 2} = 58.063, p < 0.001, power = 1$) on SWVs, with SWVs greater during adduction than at rest, and greater during flexion than during adduction. Additionally, there was a main effect of region ($F_{1,1} = 40.290, p < 0.001, power = 1$) on SWVs, with the clavicular fiber region exhibiting significantly greater SWVs than the sternocostal fiber region. Finally, there was a region × task interaction ($F_{1,2} = 9.031, p < 0.001, power = 0.972$), with the fiber regions of the pectoralis major exhibiting unique material properties depending on torque task (Figure 4.5).

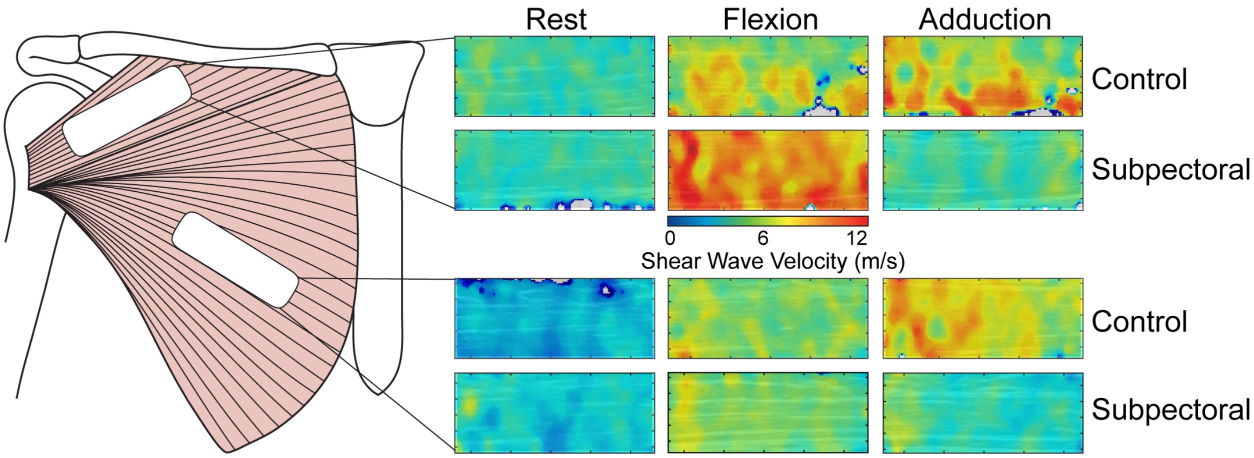

Figure 4.5 Approximate probe placement over the clavicular and sternocostal fiber regions of the pectoralis major. Representative B-Mode ultrasound images with shear wave elastography color map for each experimental group (subpectoral implant, healthy control) during each prescribed torque task (at rest, 10% MVC adduction, 10% MVC flexion).

Post hoc analyses revealed that in both experimental groups, SWVs were greater in the clavicular region than in the sternocostal fiber region during flexion (subpectoral: $p = 0.001$, healthy: $p < 0.001$) (Figure 4.6). In the healthy group, SWVs were also greater in the clavicular fiber region during adduction ($p = 0.046$). There were no differences between the fiber regions at rest in either group (subpectoral: $p = 0.309$, healthy: $p = 0.232$) and the subpectoral group did not exhibit between fiber region differences during adduction ($p = 0.210$).

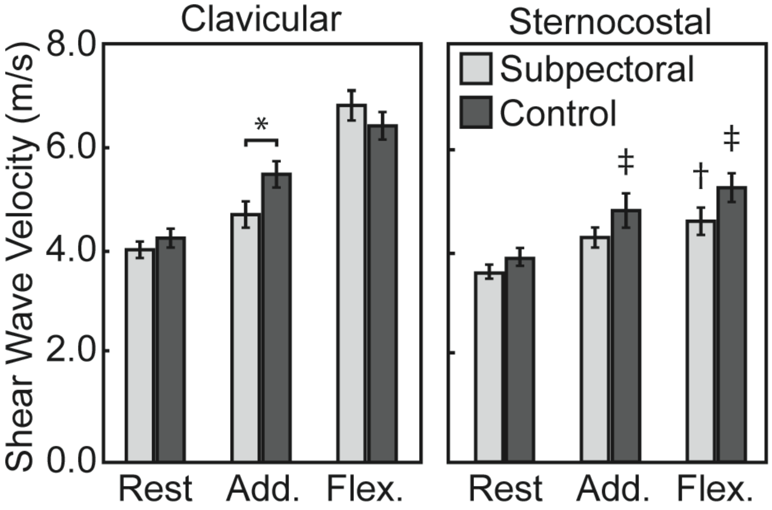

Figure 4.6 Between group differences in the material properties of the fiber regions of the pectoralis major. During SWE trials, participants remained relaxed (Rest) or produced volitional joint torques scaled to +10% MVC elevation and plane of elevation. Error bars represent mean ± standard error shear wave velocity (m/s) for each experimental group. * denotes significant between group difference. † denotes significant within group difference for the subpectoral implant group. ‡ denotes significant within group difference for the healthy control group. All significances are at the $p < 0.05$ level.

The experimental groups utilized the fiber regions of the pectoralis major differently (Figure 4.6). When producing 10% MVC adduction torques, the subpectoral implant group exhibited 15.0% lower SWVs in the clavicular region than the healthy group ($p = 0.023$). There was also a trend toward significance in the sternocostal fiber during flexion ($p = 0.056$), with the healthy group exhibiting 12.9% greater SWVs than the subpectoral implant group. No between group differences existed in the clavicular ($p = 0.505$) or sternocostal ($p = 0.398$) fiber regions when at rest. Similarly, no between group differences existed in the clavicular fiber region during flexion ($p = 0.247$), or in the sternocostal fiber region during adduction ($p = 0.124$).

Patient-Reported Outcomes

In the subpectoral implant group, several measures of shoulder joint integrity and PM material properties reached clinical significance. Decreasing shoulder abduction strength ($r = -0.679, p = 0.022$) as well as decreasing shoulder stiffness as patients generated adduction ($r = -0.729, p = 0.013$) and abduction torques ($r = -0.729, p = 0.013$) was associated with increasing SPADI score, which indicates greater shoulder pain and disability. Furthermore, increasing SWV in the clavicular ($r = 0.673, p = 0.023$) and sternocostal ($r = 0.642, p = 0.031$) fiber regions of the PM when patients were at rest were associated with increasing SPADI scores. No other metrics of shoulder joint integrity or PM material properties reached statistical significance.

4.5 Discussion

This study evaluated the joint and tissue-level implications of two-stage subpectoral implant breast reconstruction, which is the most commonly used post-mastectomy breast reconstruction procedure. Our results provide the first objective evidence that this reconstruction approach compromises the functional integrity of the shoulder joint by reducing shoulder strength and stiffness when compared to healthy age-matched controls. Our results indicate that this reconstruction approach alters function of the remaining, intact clavicular fiber region of the PM. Our results also show that patient-reported measures of shoulder strength and disability can be captured using objective and repeatable measures of shoulder strength and stiffness, and PM material properties.

Isometric measures of shoulder strength provide insights into the level of impairment experienced by subpectoral implant breast reconstruction patients. To date, only a single investigation has attempted to do so in this patient population[82]. Their results suggest that the disinsertion of the sternocostal fiber region of the PM during subpectoral implant breast reconstruction causes significant reductions in shoulder flexion, adduction, and internal rotation strength. However, the applications of their findings are limited, as their patient population was less than one year post-reconstruction, and their control participants were significantly younger than their patient population. Our use of age-matched controls and patients further removed from reconstruction provide more robust insights into the long-term implications of these surgeries. Clinical practice assumes that, given enough time to recover, the musculoskeletal system adequately compensates for the removal of shoulder musculature[118]. The subpectoral implant patients included in the current study were, on average, 20 months post-surgery. Despite this recovery period, 13 out of 14 subpectoral implant participants exhibited maximal shoulder adduction torques below the healthy control group mean, while 10 out of 14 exhibited maximal shoulder internal rotation torques below the mean for the healthy group. Our results suggest that compensatory mechanisms may not fully restore shoulder strength in this patient population.

The current study was the first to use novel, repeatable measures of shoulder stiffness to confirm that subpectoral implant breast reconstruction compromises the functional integrity of the shoulder joint. These measures of stiffness quantify a patient's ability to maintain shoulder joint stability, which provides insights into shoulder function during dynamic tasks such as activities of daily living[98]. In a single posture with the arm elevated 90 degrees, we found that both subpectoral implant patients and healthy controls exhibited similar shoulder stiffness at rest in both elevation and plane of elevation. These results are to be expected, as muscle constitutes a small contribution to overall joint stiffness at rest[175]. When producing volitional joint torques, shoulder stiffness is maintained almost entirely by the coordinated activations of shoulder musculature[102,175,176]. We found that subpectoral implant patients were unable to maintain shoulder joint stiffness when producing submaximal vertical adduction torques. These results confirm those from an investigation utilizing subjective patient-reported data that found approximately 50% of pectoralis major flap patients will experience altered shoulder stiffness[86]. Reductions in shoulder stiffness during vertical adduction could affect a variety of activities of daily living, include reaching for objects on a table. Interestingly, shoulder stiffness while producing submaximal flexion torques was not affected by the surgical disinsertion of the sternocostal region of the PM. It has been hypothesized that the clavicular, not the sternocostal fiber region, is responsible for maintaining shoulder joint stiffness in the plane of elevation[35]. Our results suggest that the intact clavicular fiber region of the PM sufficiently maintains shoulder stiffness in the plane of elevation in the absence of a portion of the sternocostal fiber region.

Our use of shear wave elastography allowed us to further investigate the tissue-level implications of subpectoral implant breast reconstruction on the material properties of the PM. We obtained SWE measurements from both fiber regions of the PM during submaximal torque generation and rest. The healthy control group exhibited similar SWVs between the fiber regions at rest, and greater SWVs in the clavicular fiber region during both adduction and flexion. The subpectoral implant group differed, as it exhibited greater SWVs in the clavicular fiber region at rest and during the generation of adduction torques, and similar between-region SWVs during the generation of flexion torques. Furthermore, we observed that when producing adduction torques, subpectoral implant patients exhibit significantly lower SWVs in the clavicular fiber region than the healthy controls. Together, these results suggest that the clavicular fibers region of the pectoralis major in subpectoral implant patients contributes more to joint stiffness at rest and during the generation of flexion torques, while it reduces its contributions to adduction torques. However, both fiber regions of the pectoralis major are being underutilized in subpectoral implant patients when compared to healthy controls. These findings contrast previous data that showed increased activity in the clavicular fiber region post-reconstruction when compared to pre-reconstruction levels during maximal voluntary contractions [119]. Future work should further investigate the long-term neuromuscular adaption of shoulder musculature to subpectoral implant breast reconstruction.

The Shoulder Pain and Disability Index clarified if the significant functional deficits identified here had an impact on a patient's activities of daily living. We found that decreasing shoulder strength and stiffness was associated with increased shoulder pain and disability. These results suggest that interventions that increase shoulder strength and stability may be beneficial for reducing post-operative patient complications. We also found that increased pectoralis major SWVs were associated with increased shoulder pain and disability. Shear wave velocity holds a strong relationship with shear modulus, and is often used as a proxy for soft tissue stiffness[177,178]. These findings suggest that reducing PM tissue stiffness may have a positive effect on breast reconstruction patients shoulder pain and disability during the execution of activities of daily living.

This study had certain limitations. Our study design did not allow us to account for the longitudinal effects of the disinsertion of the PM. We were also unable to control for the volume of muscle disinserted. We attempted to curtail this limitation by using a clinical population recruited from a single surgeon's clinic, which would insure that the procedure was performed similarly across all patients. Our testing procedures included just a single shoulder posture. This posture was chosen as it places the moment arm of both fiber regions of the PM at an optimal magnitude[147]. Finally, a single volitional torque magnitude was used for all shoulder stiffness and shear wave elastography trials. This level was chosen in an attempt to reduce the effects of fatigue.

Finally, it is unknown if patients with changes in muscle material properties observed with ultrasound SWE had underlying fatty degeneration driving these changes, as the current study did not have access to magnetic resonance imaging scans for each participant.

4.6 Conclusions

In conclusion, subpectoral implant patients experience long-term and potentially chronic deficits in shoulder strength when compared to healthy controls. Robot-assisted measures of shoulder joint stiffness indicated subpectoral implant patients do not fully recover shoulder stability, despite prolonged recovery time and substantial shoulder musculature left intact. We also observed chronic changes to the material properties of the remaining intact fiber regions of the pectoralis major following subpectoral implant breast reconstruction. Finally, many of our measures of shoulder strength and stiffness, and pectoralis major material properties were of clinical significance. In recent years, a pre-pectoral option for implant-based breast reconstruction has been introduced in order to avoid the disinsertion of the PM. The primary reason for this reconstruction option however has not been to address functional problems, but to address patient complaints of animation deformities of the breast that occur with PM contraction over implants[179,180]. Our results suggest that when possible, consideration should be given to pre-pectoral implant placement in order to avoid functional deficits arising from the disinsertion of the pectoralis major. Additionally, these results place a greater emphasis on the need to develop targeted interventions to pre- and post-operatively rehabilitate breast cancer patients that opt for an implant-based subpectoral post-mastectomy breast reconstruction.

Chapter 5. The Influence of Mastectomy and Subpectoral Implant Breast Reconstruction or Breast Conserving Therapy on the Material Properties of the Pectoralis Major

5.1 Abstract

An increasing number of women eligible for breast conserving therapy (BCT) are instead electing for mastectomy and subpectoral implant breast reconstruction. Subpectoral implant breast reconstruction and BCT uniquely influence shoulder joint function, but it is unclear to what extent these procedures differ in their effect on the integrity of the pectoralis major. The purpose of this study was to assess the influence of BCT and subpectoral implant breast reconstruction on pectoralis major material properties at rest and during the generation of shoulder torques. Shoulder strength and ultrasound shear wave elastography images were acquired from the pectoralis major of 14 BCT patients, 14 subpectoral implant patients, and 14 healthy, age-matched controls. Surface electromyography data were also obtained from six primary movers of the shoulder. BCT and subpectoral implant patients were significantly weaker in shoulder adduction, and BCT patients were weaker in internal and external rotation strength when compared to healthy controls. The material properties of the pectoralis major during the generation of shoulder torques were altered in both patient groups. Finally, BCT and subpectoral implant patients compensate for these changes using intact shoulder musculature. Women who undergo BCT or mastectomy and subpectoral implant breast reconstruction will exhibit significant long-term strength deficits of the upper extremity. These deficits are driven in part by changes to the underlying function of the

pectoralis major. Both patient groups adopt unique but inadequate neuromuscular compensation strategies at the shoulder.

5.2 Introduction

More than 1.7 million women are diagnosed with breast cancer annually worldwide. In a majority of diagnoses, the disease is localized to the breast[1]. Traditionally, diagnoses of this type are managed with breast conserving therapy (BCT), which refers to the combination of lumpectomy and radiotherapy. Lumpectomy is a surgical intervention that removes the tumor and a small volume of surrounding soft tissue. Radiotherapy is utilized post lumpectomy in order to minimize recurrence. BCT is extremely effective in neutralizing breast cancer, with fewer than 10% of BCT patients experiencing localized recurrence within 5 years[181,182]. However, an increasing number of women eligible for BCT are instead opting for mastectomy, which surgically removes all breast tissue in order to eradicate the disease[14,183]. BCT and mastectomy have equivalent recurrence rates and patient survival, suggesting that aesthetic outcome is influencing patient choice[182].

The availability of post-mastectomy breast reconstruction options may be driving the increase in patient preference of mastectomy over BCT[11,50,184]. Post-mastectomy breast reconstructions are a group of procedures that return the look and feel of natural breast tissue using a synthetic implant or autologous donor tissue from elsewhere on the body. The most common reconstructive approach elected for by early stage breast cancer patients is the immediate two-stage subpectoral implant (subpectoral implant), which accounts for more than 65% of all post-mastectomy breast reconstructions annually[37]. The first stage occurs immediately subsequent to mastectomy when the pectoralis major muscle (PM) is surgically removed from the inferior/medial pole of the breast onto the lateral border of the sternum in order to provide coverage for a temporary expander. The volume of this expander is then increased over several months before it is exchanged for a synthetic implant during the second stage.

BCT and subpectoral implant breast reconstruction are both associated with significant long-term morbidity of the shoulder [82,152,158,167]. These deficits are likely driven in part by the unique effects BCT and subpectoral implant breast reconstruction have on PM function. A greater volume of PM receives a dose of radiotherapy when compared to all other shoulder muscles[185]. Radiotherapy reduces the force-producing capacity of the PM by impairing its ability to remodel, which may lead to fibrosis and muscle atrophy [186,187]. In subpectoral implant breast reconstruction, a portion of the PM is surgically removed from its skeletal attachments, reducing its potential to contribute to shoulder function. Unfortunately, net measures of shoulder function require the contributions of all shoulder muscles, and cannot identify the effects of subpectoral implant breast reconstruction or BCT on PM function alone.

Breast cancer management often includes modalities that influence PM function. Pectoralis major function can be quantified using ultrasound shear wave elastography (SWE), an imaging technique capable of non-invasively quantifying muscle material properties [146]. When obtained at rest, PM material properties provide insight into passive muscle stiffness. During the generation of shoulder torques, PM material properties offer insight into the muscle’s contribution to shoulder function. SWE images obtained from the PM of BCT patients suggest that increasing radiotherapy dosage is associated with increasing passive PM stiffness[167]. However, little is known regarding the influence of radiotherapy on the material properties of the PM during active shoulder torque generation. In subpectoral implant patients, the PM is underutilized entirely during the generation of shoulder torques[152]. While both BCT and mastectomy and subpectoral implant breast reconstruction influence PM function, there has been no direct comparison between these treatment approaches.

Therefore, the purpose of this study was to assess the effect of subpectoral implant breast reconstruction and BCT on the material properties of the PM at rest and during the generation of planar shoulder torques. We hypothesized that BCT patients would underutilize their PM during the generation of shoulder torques when compared to subpectoral implant breast reconstruction patients and healthy, age-matched controls. We also hypothesized that subpectoral implant patients would over utilize the still intact clavicular fiber region of their PM. Findings from the current study will strengthen the surgical decision making process for early-stage breast cancer patients choosing between BCT and mastectomy with subpectoral implant breast reconstruction.

5.3 Methods

Participants

This was a retrospective, cross-sectional study investigating the influence of subpectoral implant breast reconstruction and BCT on the material properties of the PM. A review of the electronic medical record identified patients treated for primary breast cancer at the University of Michigan between 2014 and 2016. In order to control for surgical variability, subpectoral implant patients were recruited from a single surgeon's practice (A.O.M). Patients with neurologic or orthopaedic conditions of the upper extremity, previously failed breast reconstructions, or previous breast augmentations were excluded. Additionally, healthy, age-matched control participants were recruited from the University of Michigan and Ann Arbor, MI communities.

Breast-conserving therapy patients received lumpectomy, sentinel node biopsy (SLNB), and radiotherapy to the breast alone. Subpectoral implant breast reconstructions involved the disinsertion of the origin of the PM from the inferior/medial pole of the breast onto the lateral border of the sternum. When applicable, an acellular dermal matrix was used to provide inferior pole coverage. BCT patients were examined a minimum of 12 months after their final radiotherapy treatment and subpectoral implant patients were examined at least 12 months post-reconstruction. The arm treated for primary breast cancer was examined in participants who underwent unilateral breast reconstruction. In the case of bilateral reconstruction, the dominant arm was examined. Written informed consent was obtained from all participants prior to the collection of any data. All study procedures were approved by the University of Michigan's Institutional Review Board (HUM00114801, HUM00111519).

Experimental Setup

At the start of a single experimental session, participants were equipped with six single differentiated, pre-amplified (10 V/V) surface electromyography (EMG) electrodes (DE – 2.1 sensor; Bagnoli system, Delsys, Natick, MA). These electrodes obtained activity data from the following muscles: anterior (AD), medial (MD) and posterior (PD) deltoid; upper (UT) and lower trapezius (LT); latissimus dorsi (LD). The participant's skin was prepared using a combination of exfoliant gel and an alcohol swab. Each electrode was placed over the belly of the muscle (or muscle fiber region). The electrodes were parallel to the muscle fiber direction and adhered to the skin using double-sided tape. The gain was set at 1,000 for all muscles. Each muscle's signal was visually inspected to ensure sufficient signal-to-noise and no saturation.

Participants were then seated and secured to an adjustable, padded chair (Biodex Medical Systems, Shirley, New York). Movement of the torso was restricted by cushioned plates located along the low back and sides and a buckled strap across the chest. A padded, rigid cast extending from the shoulder to the hand secured the participants examined shoulder to the crank arm of a computer-controlled brushless rotary motor (Baldor Electric Company, Fort Smith, AR). The cast fixed the elbow at 90° of flexion and wrist at neutral, but the movement of the scapula was unrestricted. The rotation axis of the motor was aligned with the center of rotation of the glenohumeral joint, as approximated at the midpoint of a line connecting the acromion process to the anterior-most point of the axillary crease. Our measurement coordinate system adhered to established biomechanical protocols[138]. Participants generated isometric shoulder torques against the motor that were measured using a six-degrees-of-freedom load cell (JR3 Inc., Woodland, CA).

Pectoralis Major Material Properties

Maximal voluntary contractions (MVC) were first assessed in order to scale experimental trials to individual participant's strength. Participants repeated maximal shoulder torques in the positive and negative directions of each measurement plane (i.e. plane of elevation (Θ); elevation (Φ); rotation (Ψ)) while verbal encouragement was provided. MVCs were measured over 60 seconds, with adequate rest provided between each maximal exertion. Submaximal acclimation trials in the direction of each maximal exertion were provided before the measurement of maximal strength. Arm posture remained consistent across all experimental procedures (0° plane of elevation, 90° elevation).

Pectoralis major material properties were assessed using an Aixplorer ultrasound elastography machine (Supersonic Imagine, Aix en Provence, France) connected to a linear transducer (SL15-4, Optimization: Standard, Persistence: Medium, Smoothing: 5, Frame Rate: 12Hz). In the current study, SWV was obtained from the clavicular and sternocostal fiber regions of the PM while participants remained at rest (0% MVC) and when they generated shoulder torques scaled to 10% MVC in the positive plane of elevation (flexion) and negative elevation (adduction) directions. These torque tasks were chosen to elicit the greatest contributions from the fiber regions of the pectoralis major. Visual feedback was provided in order to ensure torque accuracy.

When obtaining elastography images of the clavicular fiber region, the transducer was located 1-2 cm inferior to the clavicle, oriented along a line connecting the sternoclavicular joint to the anterior axillary crease. When imaging the sternocostal fiber region of the PM, the transducer was initially located approximately 6 centimeters inferior to the clavicle, oriented along a line connecting the xiphoid process to the anterior axillary crease. In both cases, the transducer was translated as needed to secure its location over the belly of the clavicular fiber region. Small variations in transducer locations were necessary in order to account for individual anatomy. Satisfactory transducer orientation was confirmed when the origin and insertion of individual muscle fascicles could be identified on the B-mode image. Each B-mode image was superimposed with a 2.5 cm × 1 cm elastography color map, which provided a pixel-by-pixel measure of SWV. The size of this color map remained consistent across all participants, but its depth relative to the surface of the skin and its horizontal orientation over the image was adjusted based on individual anatomy. All images were obtained by the same experimenter and the order of all images was randomized. Two images were obtained from each fiber region (clavicular, sternocostal) during each torque task (at rest, 10% MVC flexion, 10% MVC adduction), resulting in 24 total images per participant.

Data and Statistical Analyses

Shear wave elastography images were analyzed using an established processing algorithm in MATLAB (Mathworks Inc, Natick, MA)[146,172,173]. An external trigger pedal was used to obtain each elastography image. This external trigger was also used to collect a two-second buffer (one second prior to and one second after the trigger) of EMG and shoulder torque data at the same time the image was acquired. EMG and torque data were analyzed in MATLAB. EMG data were band-passed filtered between 20-450Hz, rectified, detrended, low-pass filtered at 6Hz, averaged across the middle one second of each trial using a moving average filter with a 200ms window, and normalized to the maximal activity obtained during the MVC trial. Torque data were low-pass filtered at 500Hz with a 6th order analog Bessel filter and averaged across the middle one second of each trial using a moving average filter with a 200ms window.

All statistical tests were performed in MATLAB. Group differences in demographic variables (e.g. age, height, weight) and shoulder strength were assessed using one-way ANOVAs (anova1 function), where group (*control, BCT, subpectoral implant*) was treated as a fixed factor. Time since the last treatment was assessed using a t-test.

We tested our hypotheses 1) that BCT patients would underutilize their PM during the generation of shoulder torques when compared to subpectoral implant breast reconstruction patients and healthy, age-matched controls and 2) that subpectoral implant patients would over utilize the still intact clavicular fiber region of their PM when compared to BCT patients and healthy age-matched controls using three linear mixed effects models. In the first model, SWV was the outcome measure, group (*control, BCT, subpectoral implant*) and PM fiber region (*clavicular, sternocostal*) were fixed factors, and random intercepts controlled for variability in SWV at the subject level. Separate linear mixed models were then utilized for each fiber region of the pectoralis major (*clavicular, sternocostal*) to explore fiber region differences in SWV across our experimental groups and shoulder torques. In these models, SWV was the outcome measure, group (*control, BCT, subpectoral implant*) and shoulder torque (*flexion, adduction*) were fixed factors, and random intercepts controlled for variability in SWV at the subject level. All relevant interactions were assessed.

Finally, we performed a secondary analysis examining muscle compensation strategies at the shoulder following BCT and subpectoral implant breast reconstruction. This included the use of three linear mixed effects models. The first model examined the influence of group (*control, BCT, subpectoral implant*) and muscle (*AD, MD, PD, UT, LT, LD*) on EMG amplitude (*EMG*). The final two models assessed the influence of group (*control, BCT, subpectoral implant*) and muscle (*AD, MD, PD, UT, LT, LD*) activity on the SWV obtained from the individual fiber regions of the PM (*clavicular, sternocostal*). In all three models, subject-specific variability was controlled for using random intercepts. Bonferroni corrections for multiple comparisons were used when applicable. All analyses utilized a significance level of $p<0.05$. For one-way ANOVAs partial η^2 distinguished between small (0.010-0.059), moderate (0.060-0.0139), and large (≥0.140) clinically relevant differences[140]. For linear mixed effects models, *Cohens* f^2 identified small ($f^2 \geq 0.02$), moderate ($f^2 \geq 0.15$), and large ($f^2 \geq 0.35$) clinically relevant results[161].

5.4 Results

Participant Characteristics

A total of 42 women participated in a single experimental session. Fourteen patients who had previously been treated with BCT, 14 patients who were treated with mastectomy and subpectoral implant breast reconstruction, and 14 healthy, age-matched control participants volunteered. One-way ANOVAs revealed no significant differences in age ($F_{2,39}=1.20$, $p=0.31$), height ($F_{2,39}=0.17$, $p=0.84$), mass ($F_{2,39}=0.47$, $p=0.63$), or BMI ($F_{2,39}=1.51$, $p=0.23$) between the groups. Breast conserving therapy patients were assessed an average of 615 days post-treatment, while subpectoral implant patients were an average of 570 days post-operatively. There was no significant difference in the time between the last treatment each group received and the experimental session ($t_{1,26}=-0.99, p=0.34$). Additional demographic and clinical metrics can be found in Table 5.1.

Table 5.1 Mean (standard deviation) participant demographics for each of the three experimental groups: healthy controls (Control), breast conserving therapy (BCT), and two-stage subpectoral implant (Subpectoral).

	Control	BCT	Subpectoral	*F/t*	*p*
Number of Participants	14	14	14		
Age (yrs)	52 (5)	54 (9)	50 (10)	1.20	0.31
Height (m)	1.64 (0.1)	1.61 (0.2)	1.63 (0.1)	0.17	0.84
Weight (kg)	65 (11)	69 (21)	71 (13)	0.47	0.63
BMI (kg/m^2)	24 (2.6)	27 (6.4)	26 (4.7)	1.51	0.23
Days Post-Treatment	-	620 (206)	570 (134)	-0.99	0.34
Dominant Arm (Y/N)	14/0	9/5	11/3		
Radiation Therapy	-	14	0		
Chemotherapy	-	7	5		
Axillary Lymph Node Dissection (ALND)	-	0	0		
Sentinel Lymph Node Biopsy (SLNB)	-	14	11		

Maximal Shoulder Strength

At the onset of experimental procedures, participants repeated MVCs in the positive and negative directions of each plane of measurement. Shoulder adduction ($F_{2,39}=10.4$, $p<0.001$, $\eta^2=0.348$), internal rotation ($F_{2,39}=5.22$, $p=0.01$, $\eta^2=0.211$), and external rotation ($F_{2,39}=3.82$, $p=0.03$, $\eta^2=0.164$) strength differed significantly between our experimental groups (Figure 5.1). Multiple comparisons showed that control participants were significantly stronger than both BCT (*p<0.001*) and subpectoral implant participants (*p=0.004*) during the generation of adduction torques and significantly stronger than BCT participants during the generation of internal (*p=0.007*) and external rotation (*p=0.02*) torques. BCT and subpectoral implant participants did not differ in any measure of shoulder strength.

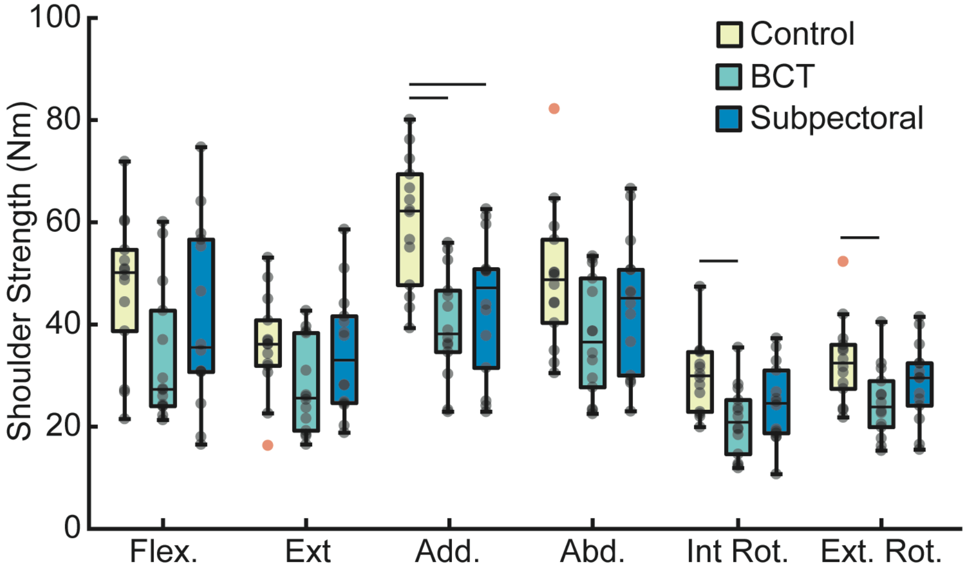

Figure 5.1 Box plots representing group median ± interquartile range differences in maximal isometric shoulder strength. Participants generated maximal shoulder torques in the positive and negative directions in elevation (adduction, abduction), plane of elevation (flexion, extension), and rotation (internal rotation, external rotation). Individual subject data are represented as transparent black dots, while outliers are represented as transparent red dots. Horizontal bars represent significant between-group differences at $p < 0.05$.

Pectoralis Major Material Properties

Next, we obtained ultrasound shear wave elastography images from both fiber regions of the PM while participants remained at rest, or maintained shoulder torques scaled to 10% of their maximum shoulder flexion and adduction strength. Shear wave elastography images were obtained from each fiber region of the pectoralis major while participants remained at rest, or generated shoulder torques scaled to 10% of their maximal strength in shoulder flexion and adduction. Representative shear wave elastography images obtained from a representative participant in each of our experimental groups can be found in Figure 5.2. In this visualization, cooler colors are representative of lower shear wave velocities, which represent a less stiff muscle at rest, and a less active muscle during volitional contraction. Visually, it appears that the included BCT participant underutilized both regions of the pectoralis major during the generation of flexion and adduction torques when compared to the representative healthy participant. Conversely, the included subpectoral implant participant over utilized the clavicular fiber region of the pectoralis major during the generation of flexion torques and underutilized the sternocostal fiber region during the generation of adduction torques when compared to the representative healthy participant.

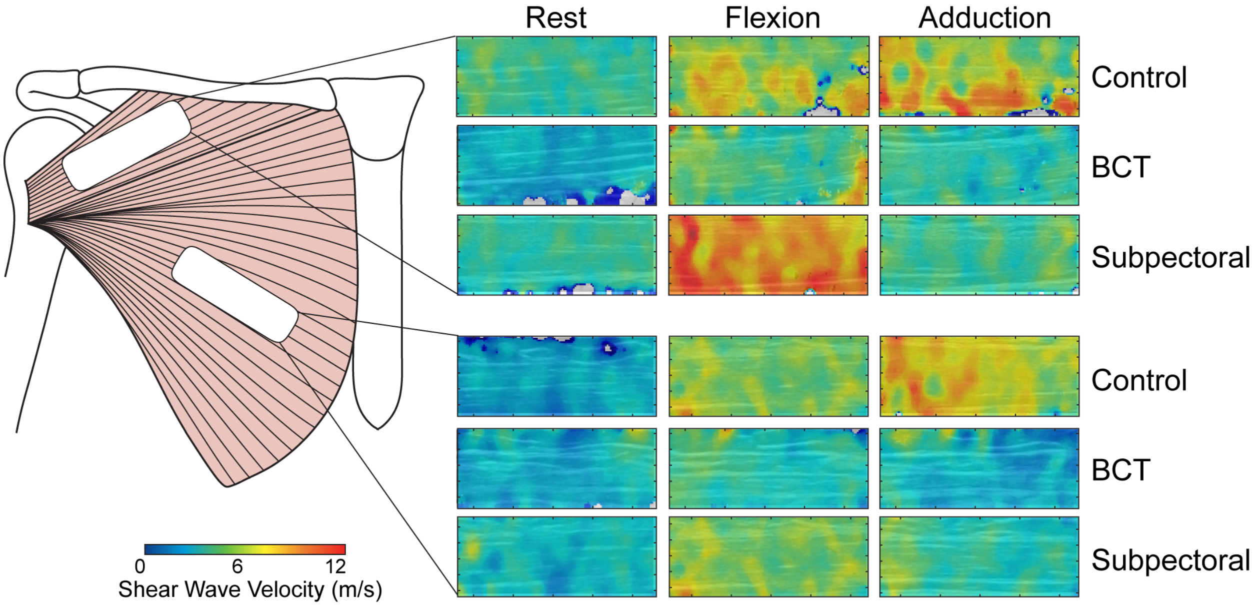

Figure 5.2 Schematic of shear wave elastography probe placement and imaging protocol. Participants remained at rest, or generated and maintained shoulder torques scaled to 10% of their maximal voluntary strength in shoulder adduction or flexion. Visual feedback was provided in order to ensure torque accuracy. During each experimental task, shear wave elastography images, pictured here as representative B-Mode ultrasound images overlaid with shear wave elastography color maps, were obtained from the fiber regions of the pectoralis major in each of our three experimental groups.

We then assessed how experimental group and fiber region influence SWV magnitude. This assessment described experimental data well ($R^2=0.57$). We found that SWV was influenced by fiber region ($F_{1,898}=47.6, p<0.001, f^2=0.001$) and group ($F_{2,892}=5.78, p=0.003, f^2=0.16$). SWV magnitude was greater in healthy controls and subpectoral implant patients than in BCT patients (both $p\leq 0.009$). Across groups, the clavicular fiber region exhibited significantly greater SWV than the sternocostal fiber region. This model also revealed a group × fiber region ($F_{2, 898}=5.68$, $p=0.003, f^2=0.011$) interaction (Figure 5.3). The SWV obtained from the clavicular fiber region of control and subpectoral implant participants was significantly greater when compared to BCT participants (*both* $p\leq 0.035$).

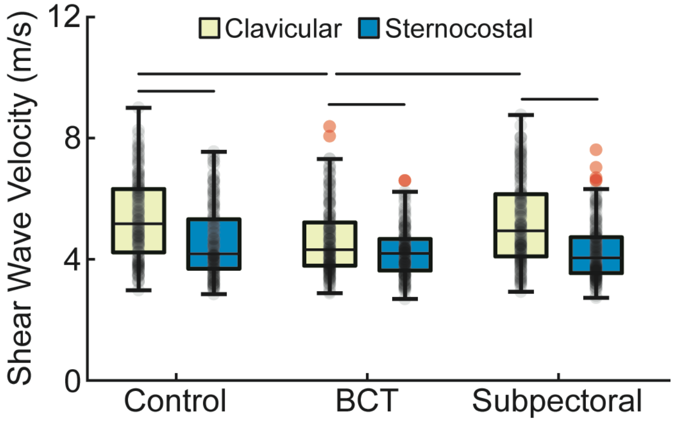

Figure 5.3 Boxplots of group (median ± interquartile range) differences in pectoralis major material properties across pectoralis major fiber region. Individual subject data are represented as transparent black dots, while outliers are represented as transparent red dots. Significant differences at $p < 0.05$ are represented as horizontal bars.

We then assessed the influence of the experimental group and shoulder torque on SWV obtained from the individual fiber regions of the pectoralis major. These assessments described experimental data well (*clavicular:* $R^2=0.69$, *sternocostal:* $R^2=0.57$). We found that SWV obtained from both fiber regions increasing significantly with increasing shoulder torque magnitude in flexion and adduction (all $F_{2,451}\geq 35.5, p\leq 0.001, f^2\geq 0.20$). In the clavicular region, we observed group × flexion torque magnitude ($F_{2,451}=3.91$, $p=0.021$, $f^2=0.015$) and group × adduction torque magnitude ($F_{2,451}=3.31, p=0.037, f^2=0.009$) interactions (Figure 5.4). Clavicular fiber region SWV was significantly greater with increasing shoulder adduction torque magnitude in control participants when compared to BCT (*p=0.025*) or subpectoral implant participants (*p=0.049*). Clavicular fiber region SWV was significantly greater with increasing shoulder flexion torque magnitude in subpectoral implant patients when compared to healthy controls (*p=0.016*). In the sternocostal fiber region, we observed a group × flexion torque magnitude ($F_{2,\ 435}=7.03$, $p<0.001$, $f^2=0.031$) interaction. Sternocostal fiber region SWV was significantly greater with increasing flexion torque magnitude in controls when compared to BCT (*p=0.001*) or subpectoral implant participants (*p=0.002*).

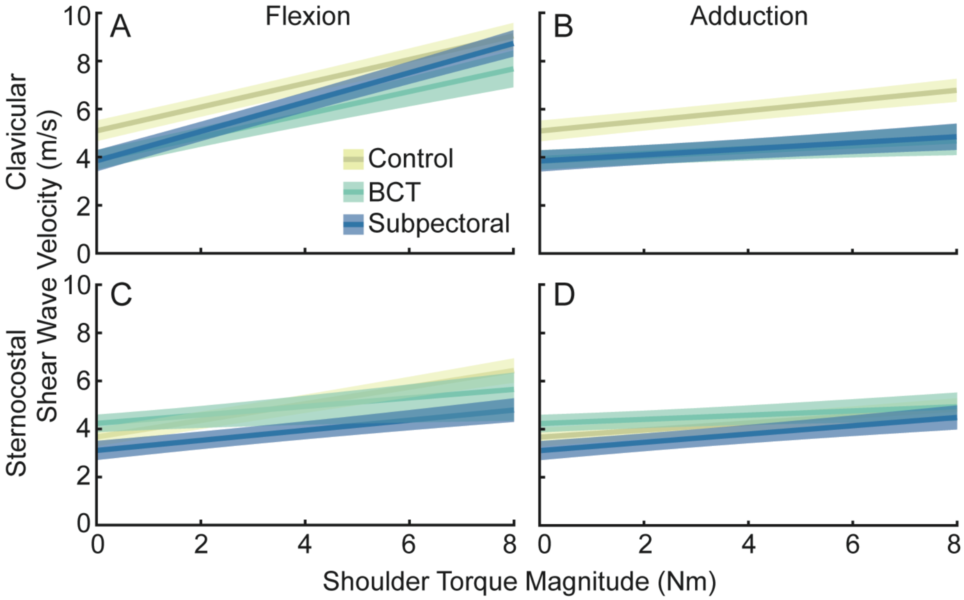

Figure 5.4 The influence of shoulder torque magnitude on mean shear wave velocity obtained from the clavicular (A,B) and sternocostal (C,D) fiber regions of the pectoralis major during the generation of flexion (A,C) and adduction (B,D) torques. Lines represent the resultant linear mixed model fits for each experimental group. Shaded regions indicate 95% confidence intervals.

Muscle Compensation Strategies

We performed a secondary analysis identifying muscle compensation strategies adopted by BCT and subpectoral implant breast reconstruction participants. This analysis examined the influence of group on surface EMG amplitude obtained from six primary movers of the shoulder

(Figure 5.5). This analysis revealed a statistically significant main effect of muscle ($F_{5,5334}=36.6$, $p<0.001$, $f^2=0.12$), but there was no significant main effect of group ($F_{2,5334}=0.63$, $p=0.53$, $f^2=0.04$). A group × muscle interaction was also observed ($F_{10,5334}=18.1$, $p<0.001$, $f^2=0.032$). The subpectoral implant group exhibited significantly greater upper and lower trapezius activity when compared to both BCT and control participants (*all* $p\leq0.04$). The control group exhibited significantly greater latissimus dorsi activity when compared to both the BCT ($p=0.047$) and subpectoral implant ($p<0.001$) participants.

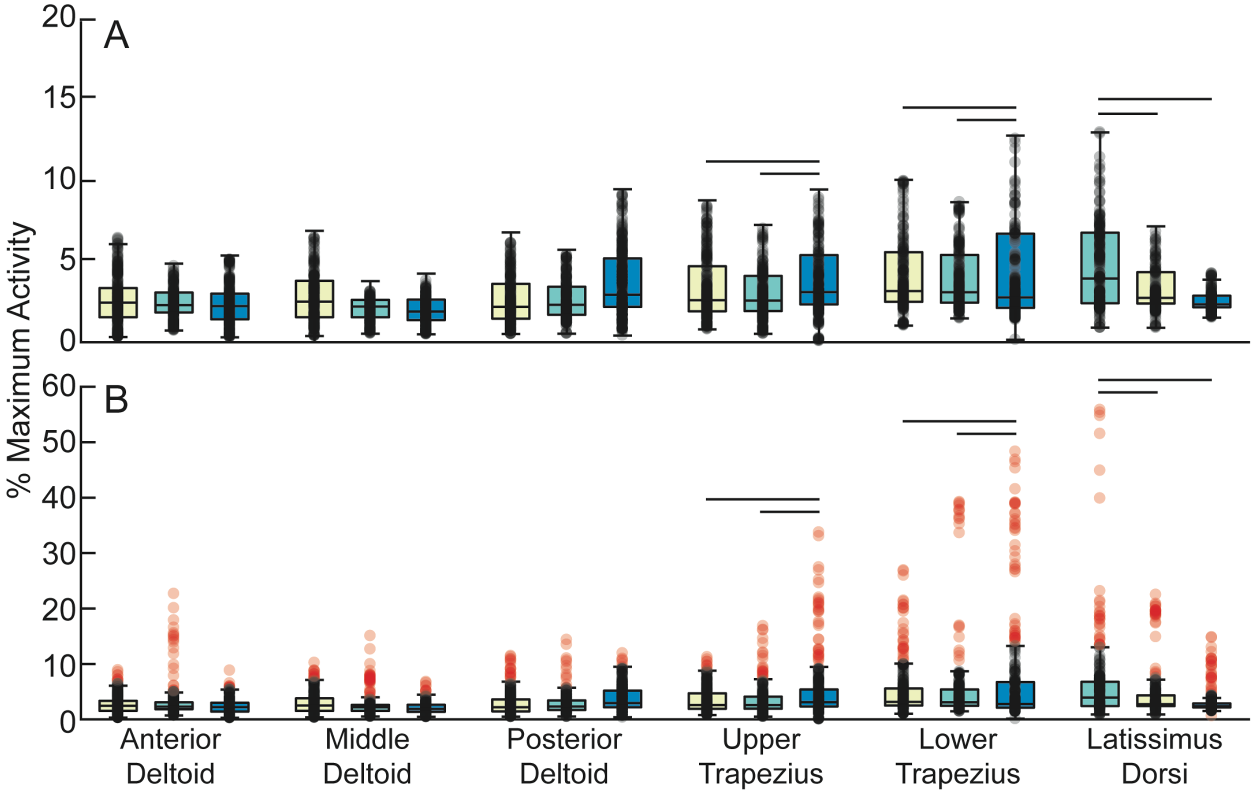

Figure 5.5 Boxplots of group (median ± interquartile range) differences in shoulder muscle activity. In figure A, individual subject data are represented as transparent black dots, with outliers removed to improve visibility. Outliers are included in figure B. Significant differences at p < 0.05 are represented as horizontal bars.

Our secondary analysis also included an assessment of the influence of group and muscle on the SWV obtained from the individual fiber regions of the PM. This analysis revealed a main effect of anterior deltoid (*clavicular:* $F_{1,421}=9.1$, $p=0.003$, $f^2=0.08$; *sternocostal:* $F_{1,405}=19.3$, $p<0.001$, $f^2=0.06$) and upper trapezius (*clavicular:* $F_{1,421}=22.4$, $p<0.001$, $f^2=0.20$; *sternocostal:* $F_{1,405}=29.7$, $p<0.001$, , $f^2=0.11$) EMG amplitude in both fiber regions. In each of these cases, SWV increased with increasing EMG amplitude. Group × posterior deltoid ($F_{2,421}=3.94$, $p=0.020$, $f^2=0.146$), group × upper trapezius ($F_{2,421}=11.7$, $p<0.001$, $f^2=0.052$), and group × lower trapezius ($F_{2,421}=6.84$, $p=0.001$, $f^2=0.007$) interactions were observed in the clavicular fiber region. SWV obtained from the clavicular fiber region was significantly greater with increasing posterior deltoid activity in subpectoral implant participants ($p=0.014$) when compared to control participants (Figure 5.6). Clavicular fiber region SWV was significantly greater with increasing upper trapezius activity in control participants when compared to both BCT ($p<0.001$) and subpectoral implant participants ($p<0.001$), and was also significantly greater with increasing lower trapezius activity when compared to BCT participants ($p=0.014$). Group × anterior deltoid ($F_{2,405}=3.54$, $p=0.030$, $f^2=0.018$) and group × upper trapezius ($F_{2,405}=14.5$, $p<0.001$, $f^2=0.096$) interactions were observed in the sternocostal fiber region. SWV obtained from the sternocostal fiber region was significantly greater with increasing anterior deltoid activity in control participants when compared to BCT participants ($p=0.01$) and was also significantly greater with increasing upper trapezius activity in control participants when compared to subpectoral implant participants ($p<0.001$).

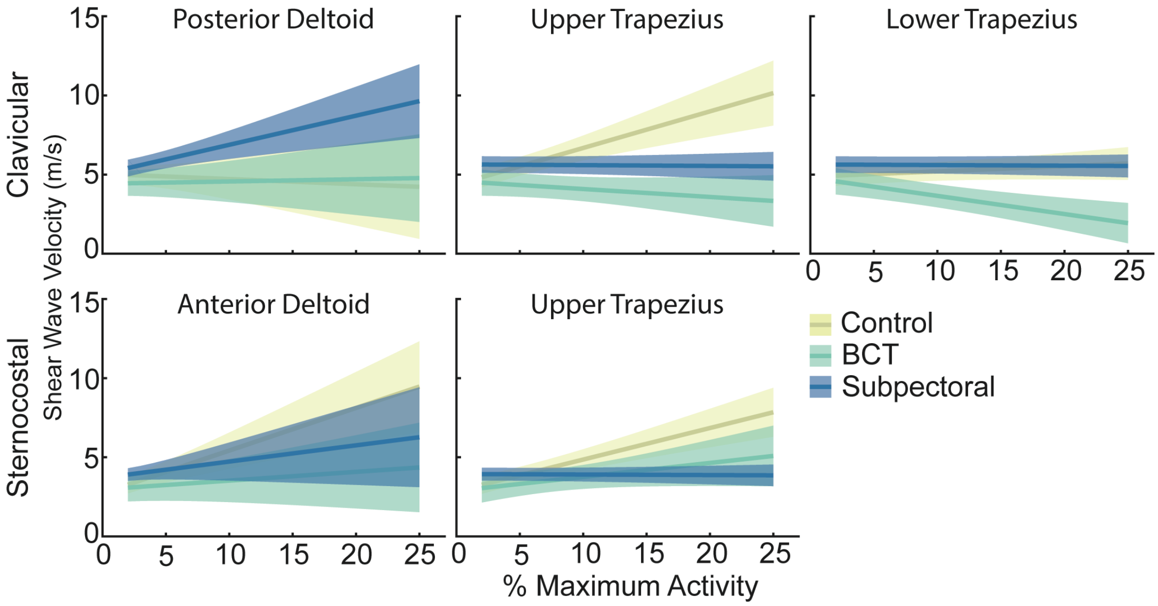

Figure 5.6 The influence of select shoulder muscle activity on mean shear wave velocity obtained from the clavicular (top row) and sternocostal (bottom row) fiber regions of the pectoralis major. Lines represent the resultant linear mixed model fits for each experimental group.

5.5 Discussion

This study investigated the influence of BCT and mastectomy and subpectoral implant breast reconstruction on the material properties of the PM. Additionally, this study was the first of its kind to investigate shoulder muscle compensation strategies adopted by BCT and subpectoral implant breast reconstruction patients. We found that BCT and subpectoral implant participants both exhibit significantly reduced shoulder strength in adduction when compared to healthy participants, while BCT participants also exhibit significantly reduced internal and external rotation strength. We also found that BCT and subpectoral implant participants utilize their PM uniquely when compared to healthy participants. Both BCT and subpectoral implant participants underutilize the clavicular fiber region of the PM during the generation of shoulder adduction torques and underutilize the sternocostal fiber region during the generation of flexion torques. Additionally, subpectoral implant participants appear to increase the contributions of the clavicular fiber region during the generation of flexion torques when compared to healthy controls. Finally, a secondary analysis of EMG obtained from six primary movers of the shoulder revealed that BCT and subpectoral implant participants utilize altered shoulder muscle activation patterns when compared to healthy participants.

Adequate shoulder strength is critical to the performance of activities of daily living. Previous investigations into the effect of BCT and subpectoral implant breast reconstruction on shoulder strength suggest that both approaches reduce shoulder strength in adduction when compared to healthy participants[82,152,167]. Our results confirm these findings and further found BCT patient's exhibit reduced internal and external rotation strength. The strength deficits observed in BCT and subpectoral implant patients are likely driven by compromised PM function. A vital element of BCT is radiotherapy to the entire breast, during which both fiber regions of the PM receive a large dose. Radiotherapy may reduce the force-producing capacity of the PM by damaging satellite cells and impairing myoblast proliferation[186,187]. The fiber regions of the PM combine to assist the shoulder in flexion, adduction, and internal rotation [147,157]. Reduced shoulder strength in one or more of these actions is to be expected if the function of both fiber regions of the PM is altered following radiotherapy. Subpectoral implant breast reconstruction patients avoid radiotherapy due to its adverse effects on soft tissue. However, this reconstructive approach requires the disinsertion of the sternocostal fiber region of the PM from its bony attachments. The sternocostal fiber region is primarily responsible for assisting in shoulder adduction, and its disinsertion renders it inoperative. The participants utilized in the current study were, on average, more than 18 months post-treatment. Clinical dogma suggests that patients recover entirely that far post-treatment[61,62,118,133] . However, our results indicate that BCT and subpectoral implant breast reconstruction patients may not ever recover adequate shoulder strength.

Shear wave elastography offers a precise, repeatable method for the quantification of PM material properties. Previous investigations into the material properties of the PM in BCT participants suggest that PM material properties are largely unchanged relative to healthy controls[167]. Following subpectoral implant breast reconstruction, clavicular fiber region material properties are significantly reduced during shoulder adduction when compared to healthy controls, indicating reduced contribution[152]. We obtained SWE images from both fiber regions of the PM while participants remained at rest, or generated shoulder torques in flexion and adduction. Our results indicate that the contribution of the clavicular fiber region of the PM is significantly reduced in BCT participants when compared to healthy controls and subpectoral implant breast reconstruction participants. Our examination of the relationship between shoulder torque magnitude and individual PM fiber region material properties allowed us to further examine the impact of BCT and subpectoral implant breast reconstruction on PM function. We observed that in all three groups, clavicular fiber region SWV increased with increasing flexion torque magnitude and sternocostal fiber region SWV increased with increasing adduction torque magnitude. This is to be expected based on the anatomy of the pectoralis major, as the clavicular fiber region's largest moment arm is in flexion, while the sternocostal fiber region's largest moment arm is in adduction[147,157]. However, we found that healthy control participants utilize the clavicular fiber region more during the generation of shoulder adduction torques and the sternocostal fiber region more during the generation of flexion torque when compared to BCT or subpectoral implant participants. This suggests that in healthy participants, the entire PM contributes to shoulder function, whereas the individual fiber regions contribute only to their primary function in BCT and subpectoral implant participants. Additionally, we found that subpectoral implant patients utilize the clavicular fiber region more during flexion than controls. Because the clavicular fiber region is the only intact fiber region in subpectoral implant participants, it is unsurprising that it increases its contributions to shoulder function. Together these results indicate that PM function is fundamentally altered following BCT and subpectoral implant breast reconstruction.

The PM is a major contributor to shoulder function. It is the third-largest shoulder muscle by volume and one of only four muscles that possess adduction moment arms[147,157,188]. Remaining, intact shoulder musculature must increase their contributions if shoulder function is to be maintained after BCT or subpectoral implant breast reconstruction. However, there is a paucity of data regarding the muscle compensation strategies adopted by patients following these treatments for breast cancer. We examined surface EMG from six primary movers of the shoulder during the generation of shoulder flexion and adduction torques. An analysis of their activity revealed increased upper and lower trapezius muscle activity in subpectoral implant breast reconstruction patients when compared to healthy controls and BCT patients. In an intact shoulder, the fiber regions of the trapezius actuate the scapula or fix it in place when co-contracted alongside the serratus anterior [189]. They may also act as antagonists to the pectoralis major when maintaining shoulder and scapular stiffness. Subpectoral implant breast reconstruction reduces shoulder stiffness, a measure that is closely related to clinical assessments of shoulder stability [152]. Our results suggest that subpectoral implant patients may compensate for reduced shoulder stiffness by increasing trapezius activity. Additionally, control participants exhibited greater latissimus dorsi activity when compared to BCT and subpectoral implant patients. The latissimus dorsi is one of the largest shoulder muscles and a primary contributor to shoulder adduction like the PM [147,157,188]. Because of the direct impact of BCT and subpectoral implant breast reconstruction on PM function, it is reasonable to believe that both groups would avoid forcefully adducting the arm. If this is the case, it is possible that the latissimus dorsi loses its force-producing capacity through disuse. This hypothesis is supported by our finding that BCT and subpectoral implant patients exhibit significantly reduced shoulder strength in adduction when compared to healthy participants. We expanded our investigation into muscle compensation strategies by examining the relationship between the activity in remaining, intact shoulder muscles and SWV obtained from each fiber region of the PM. This analysis revealed coactivation between the PM and trapezius muscle in healthy control participants that were absent in BCT and subpectoral implant patients. Additionally, we found that SWV obtained from the clavicular fiber region of the PM increased more significantly with increasing posterior deltoid activity in subpectoral implant patients when compared to healthy participants. The posterior deltoid acts as an antagonist to the pectoralis major, suggesting that subpectoral implant patients may recruit the posterior deltoid to compensate for reductions in trapezius muscle activity.

The current study has limitations that may influence the interpretation of our findings. Our results yielded varied effect sizes, which limits the scope of these results. For example, our strength results were associated with large ($\eta^2 \geq 0.140$) effect sizes, while our results assessing the relationship between pectoralis major material properties and upper extremity muscle activations yielded small to moderate ($0.02 \leq f^2 \leq 0.149$) effect sizes. The design of future studies should attempt to mitigate these power issues. We attempted to improve the impact of our research by using well-defined, homogeneous groups with respect to clinical treatment plans. However, the pre-treatment status of the included participants is unknown. Our limited sample size inhibited our ability to include arm dominance in our statistical model. We were also unable to control for the volume of PM disinserted during subpectoral implant breast reconstruction. Reconstruction patients from a single surgeon's practice in an attempt to minimize the effect of this limitation. Our experimental protocol included the use of only a single arm posture. This posture was chosen as it places both fiber regions of the PM at an optimal operating length[147,157,190,191]. Additionally, participants generated shoulder torques at only a single magnitude. Our analysis treated torque magnitude as a continuous variable in order to control for this limitation. Finally, magnetic resonance images were not available for the included patients, so it is unknown if the patients included in the current study had fatty degeneration driving altered PM material properties.

5.6 Conclusions

Women who undergo BCT or mastectomy and subpectoral implant breast reconstruction will exhibit significant long-term strength deficits of the upper extremity when compared to healthy, age-matched controls. Our findings suggest that these deficits are driven in part by changes to the underlying function of the fiber regions of the PM. Finally, these clinical groups adopt unique albeit inadequate muscle compensation strategies at the shoulder. Together, these results highlight the need to monitor and restore PM function in patients undergoing BCT or subpectoral implant breast reconstruction. Additionally, our results emphasize the need for pre- and post-treatment rehabilitation protocols that address remaining, intact shoulder musculature in addition to the PM.

Chapter 6. Neuromuscular Compensation Strategies Adopted at the Shoulder Following Bilateral Subpectoral Implant Breast Reconstruction

6.1 Abstract

Immediate two-stage subpectoral implant breast reconstruction after mastectomy requires the surgical disinsertion of the sternocostal fiber region of the pectoralis major (PM). The disinsertion of the PM would require increased contributions from intact shoulder musculature in order to generate shoulder torques. The aim of this study was to identify neuromuscular compensation strategies adopted by subpectoral implant breast reconstruction patients using novel muscle synergy analyses. Fourteen patients treated bilaterally with subpectoral implant breast reconstruction (>2.5 years post-reconstruction) were compared to ten healthy controls. Surface electromyography was obtained from sixteen shoulder muscles while participants generated eight three-dimensional shoulder torques in five two-dimensional arm postures bilaterally. Non-negative matrix factorization revealed the muscle synergies utilized by each experimental group on the dominant and non-dominant limbs, while the normalized similarity index assessed group differences in overall synergy structure. Bilateral subpectoral implant patients exhibited similar shoulder strength to healthy controls on the dominant and non-dominant arms. Our results also suggest that three-dimensional shoulder torque is driven by three shoulder muscle synergies in both healthy participants and subpectoral implant patients. Two out of three synergies were more similar than is expected by chance between the groups on the non-dominant arm, whereas only one synergy is more similar than is expected by chance on the dominant arm. While bilateral

shoulder strength was maintained following bilateral subpectoral implant breast reconstruction, a closer analysis of these synergy patterns reveal subpectoral implant patients adopted compensatory neuromuscular strategies only with the dominant arm.

6.2 Introduction

An increasing number of women will have their primary breast cancer managed with mastectomy, a surgical procedure that removes all breast tissue in order to eradicate the disease [18,192]. The increase in this mastectomy rate is driven in part by the availability of post-mastectomy breast reconstruction options [11,50,184,193,194]. Post-mastectomy breast reconstructions are a family of surgical procedures that utilize an artificial implant or autologous soft tissue to restore volume to the breast. Two-stage subpectoral implant (subpectoral implant) breast reconstruction accounts for approximately 69% of all post-mastectomy breast reconstructions [37]. The first stage of subpectoral implant breast reconstruction occurs in the same procedure as mastectomy. The sternocostal fiber region of the pectoralis major (PM) is released from the inferior/medial pole of the breast onto the sternum to allow for the placement of a tissue expander beneath the muscle. The volume of this expander is increased systematically over several months, increasing the subpectoral space to the desired implant size. The second, far less invasive stage involves exchanging the expander for a permanent implant.

An intact PM is critical for the generation of shoulder flexion, adduction, and internal rotation torques and the maintenance of shoulder stiffness [91,147,157,190,191]. The disinsertion of the PM leads to significant reductions in shoulder strength, as well as reduced shoulder stiffness during the maintenance of adduction torques[81,82,152,195]. Clinical practice assumes that remaining, intact shoulder musculature increases their contributions to shoulder function following the disinsertion of the pectoralis major[118]. Surface electromyography (sEMG) obtained from the fiber regions of the PM before and after subpectoral implant breast reconstruction suggest that the clavicular fiber region increases its contribution in the absence of a functioning sternocostal fiber region [119]. When compared to healthy, age-matched participants, shear wave elastography obtained from the fiber regions of the PM at rest and during contraction suggest that the entire muscle reduces its contributions to shoulder function[119,152]. It remains unknown how remaining, intact shoulder musculature compensates for the removal of a portion of the PM.

The shoulder complex is a highly indeterminate system, where nearly identical shoulder torques can be produced by altering the timing and magnitude of synergist muscles. The central nervous system (CNS) simplifies the solution space for such a problem by activating low-dimensional groups of muscle, henceforth referred to as muscle synergies, using a single neural command [196-198]. Muscle synergies are commonly derived using a computational technique that decomposes experimental sEMG data into a set of synergy vectors that describe the weighted contributions of a given number of muscles to a set of experimental tasks. Overall muscle synergy structure remains robust across healthy participants during unilateral reaching tasks but is influenced by handedness[199-203]. Healthy participants will generate similar shoulder torques using different muscle activations on their dominant and non-dominant limbs. Clinical conditions affecting the nervous system, such as stroke and cerebral palsy, will also alter shoulder muscle synergy structure[204-206]. These pathologic conditions result in reduced neuromuscular complexity, as evidenced by fewer synergies required to adequately describe experimental sEMG data [206,207]. Attempts to restore neuromuscular complexity in cerebral palsy patients using multi-level orthopaedic surgery have been unsuccessful[208]. However, it is unknown how subpectoral implant breast reconstruction surgeries influence the muscle synergies underlying shoulder torque generation.

Therefore, the purpose of this study was to examine the neuromuscular compensation strategies adopted by patients previously treated with mastectomy and subpectoral implant breast reconstruction. We hypothesized that subpectoral implant breast reconstruction patients would exhibit altered surface EMG activation amplitudes when compared to healthy controls. We also hypothesized that the structure of shoulder muscle synergies derived from subpectoral implant breast reconstruction patients would differ from those derived from healthy participants, regardless of the arm in which the reconstruction was performed. Finally, we hypothesized that neuromuscular complexity would be reduced in subpectoral implant breast reconstruction patients on both the dominant and non-dominant arms.

6.3 Methods

Participants

The current study examined neuromuscular compensation strategies adopted by subpectoral implant breast reconstruction patients. Twenty-four women participated in a single experimental session. Fourteen women who had previously received a mastectomy and subpectoral implant breast reconstruction at the University of Michigan between 2014 and 2017 were identified through a retrospective review of the electronic medical record. In order to control for between-participant variability in surgical technique, participants were recruited from a single surgeon's practice (A.O.M). All participants had the sternocostal fiber region of the pectoralis major disinserted from the inferior and medial pole of the breast onto the sternum. Participants were examined a minimum of 18 months post-reconstruction. Ten healthy participants were recruited from the Ann Arbor and University of Michigan communities. Participants with a history of neuromuscular or orthopaedic conditions of the upper extremity were excluded. Additionally, subpectoral implant patients who had previously undergone radiotherapy for primary breast cancer, patients with previously failed breast reconstructions, or patients who had undergone a breast augmentation surgery prior to mastectomy were excluded. Participants provided written informed consent prior to the collection of any data. Study procedures were approved by the University of Michigan's Institutional Review Board (HUM00114801 and HUM00111519).

Experimental Procedures

Experimental procedures were completed in a single, 120-minute session. Both arms were examined with the order randomized. Participants were secured to a custom-built chair (Biodex Medical Systems, Shirley, New York) equipped with padded plates along the sides and lower back and a padded strap for across the chest to ensure minimal torso movement. The arm under examination was secured to the crank arm of a computer-controlled brushless rotatory motor (Baldor Electric Company, Fort Smith, AR) via a padded, removable plastic cast. The cast fixed participants elbows in 90° of flexion and wrist in neutral. The axis of rotation of the motor was aligned with the axis of rotation of the glenohumeral joint, estimated at the midpoint of a line connecting the anterior axillary crease to the acromioclavicular joint. Our coordinate system complied with international biomechanical standards (motion of the humerus relative to the thorax (Y-X-Y order)) [138]. The crank arm of the motor resisted participants as they produced isometric shoulder torques, while torque magnitudes were measured using a six degrees-of-freedom load cell (JR3, Inc., Woodland, CA). The motor was controlled in real-time using MATLAB Simulink Real Time (2016a, Mathworks Inc, Natick, MA) with all analog data sampled at 2,500 Hz.

Activation data were obtained from 16 shoulder muscles using single differentiated, pre-amplified (10 V/V) surface EMG electrodes (DE – 2.1 sensor; Bagnoli system, Delsys, Natick, MA). The sixteen muscles included: the sternocostal (SC) and clavicular (CL) fiber regions of the pectoralis major; anterior (AD), medial (MD) and posterior (PD) deltoid; upper (UT), middle (MT), and lower trapezius (LT); latissimus dorsi (LD), teres major (TM), infraspinatus (IF), serratus anterior (SA), biceps brachii long head (BI), brachioradialis (BR); triceps brachii long (TriLg) and lateral heads (TriLt). Prior to the placement of electrodes, the participant's skin was prepared using a combination of exfoliant gel and an alcohol swab. Electrodes were placed over the belly of the muscle/muscle fiber region, oriented parallel to the direction of muscle fibers. The gain was set to 1,000 for all muscles and each signal was visually inspected prior to the collection of data to ensure adequate signal-to-noise and minimal saturation.

Maximal voluntary contractions (MVC) were obtained at the onset of experimental procedures in order to scale all experimental tasks to individual participant's strength. MVCs were obtained in a single posture, with the arm in 15° of plane of elevation and 75° elevation. Maximal shoulder muscle strength is largely posture-dependent[209]. The posture used in the current study was chosen to avoid the fatigue induced by repeated maximal contractions in multiple postures. Participants generated maximal isometric shoulder torques in the positive and negative direction of each plane of measurement (plane of elevation (Θ); elevation (Φ); rotation (Ψ)) for six repetitions. In order to ensure maximal exertion, verbal motivation was provided and adequate rest was encouraged. Additionally, participants were given the opportunity to perform submaximal practice trials prior to the acquisition of MVCs.

Participants were examined bilaterally in five arm postures: 15° plane of elevation combined with 75° elevation and every combination two plane of elevation (0°, 45°) and elevation

(45°, 105°) angles (Figure 6.1). These postures were chosen as they represented the center and outer edges of a normal upper extremity workspace. The base of the custom-built chair rotated in 15° increments, which controlled the plane of elevation angle. The elevation angle was manipulated by repositioning the crank arm of the motor, which was controlled by a high precision encoder. The order in which arm postures were examined was randomized within each arm. In each arm posture, participants generated and maintained 3-dimensional shoulder torques for two seconds in every combination of shoulder plane of elevation ($\pm\mathit{\Theta}$), elevation ($\pm\mathit{\Phi}$), and rotation ($\pm\mathit{\Psi}$). Each component was scaled to the participant's lowest recorded MVC to ensure satisfactory execution and the avoidance of fatigue. The order in which torques were presented within each arm posture was randomized. Visual feedback was provided by an LCD display to assist participants with torque accuracy. This feedback presented as a blank, white screen, a small dashed box, and a small red box. Participants controlled the red square using isometric shoulder torques, while the position of the dashed box represented the prescribed magnitude and direction of each 3-dimensional torque task. Adequate rest was provided between trials. In total, participants matched eight torque tasks in five arm postures on both arms, for a total of 80 individual trials.

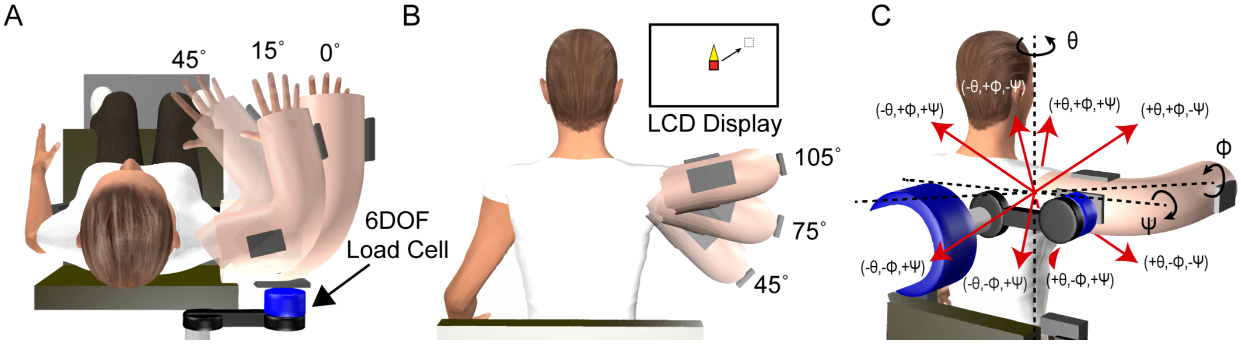

Figure 6.1 Schematic of the experimental setup, arm postures, and three-dimensional isometric shoulder torques. Each participant's dominant and non-dominant shoulders were assessed in five arm postures that were a combination of plane (A) and elevation (B) positions. In each posture, participants generated three-dimensional shoulder torques in every combination of ± plane of elevation (Θ), ± elevation (Φ), and ± rotation (Ψ) (C). Visual feedback was provided via an LCD display to assist with torque accuracy.

Data Analyses

Surface electromyography data were analyzed in MATLAB 2017a (Mathworks Inc, Natick, MA). Data were band-pass filtered between 20 and 450 Hz, rectified, detrended, low-pass filtered at 6 Hz, averaged using a moving average filter with a 200ms window, and normalized to the muscle's maximum obtained during MVCs.

The muscle synergies underlying three-dimensional shoulder torque generation were derived using non-negative matrix factorization (NNMF) in MATLAB (nnmf, alternating least squares). This analysis decomposes a matrix of experimental data (A) into synergy (W) and coefficient (C) matrices by minimizing the root-mean-squared error between experimental (A) and reconstructed data ($W \cdot C$). The dimensions of synergy matrices are a function of the number of included muscles (16) and a user-defined variable that represents the number of synergies (N_W). Our analysis was iterated with N_W beginning at one and increasing by one until reconstructed data accounted for more than 95% of the variance in experimental data. In order to avoid local minima, we repeated this analysis 10 times for each participant and arm, yielding 460 (23 participants × 2 arms × 10 repetitions) unique sets of synergies. The number of synergies required to account for more than 95% of the variance in experimental data (N_{95}) differed by participant and arm.

Non-negative matrix factorization results in a synergy matrix in which synergies are ordered from first to last according to the total variance in experimental data they account for. The first, or principle synergy ($tVAF_1$), accounts for the greatest variance in experimental data, with each subsequent synergy contributing by a diminishing degree. The order in which synergies are presented will depend on participant and arm. Therefore, the comparison of synergies across arms and experimental groups required a custom written organization algorithm previously described in the literature. This algorithm utilizes the normalized similarity index (SI), which represents the cosine of the angle between two synergy vectors. The SI is reported on a scale from 0-1, where 1 means two synergies are identical. The minimum SI to determine if two synergies were more similar than is expected by chance was set at 0.63, which corresponds to the critical value of Pearson's r at $p=0.01$ for 14 degrees of freedom (16 muscles – 2).

Statistical Analysis

All statistical tests were performed in SPSS (v24, IBM Corporation, Chicago, IL, USA). T-tests examined group differences in demographic variables. Shoulder strength was assessed using separate linear mixed effects models for each strength measure (*flexion, extension, adduction, abduction, internal rotation, external rotation*) where arm dominance (*dominant, non-dominant*) and experimental group (*control, subpectoral implant*) were fixed factors and random intercepts controlled for variability at the subject level. All relevant interactions were assessed.

To test our hypothesis that subpectoral implant breast reconstruction patients would exhibit altered surface EMG activation amplitudes when compared to healthy controls, we utilized three separate linear mixed effects models for each shoulder muscle. In the first model, arm dominance (*dominant, non-dominant*) and experimental group (*subpectoral implant, control*) were fixed factors, and EMG amplitude (*EMG*) was the outcome measure. The second and third models for each muscle assessed data obtained individually from the dominant and non-dominant arms. In these models, experimental group (*subpectoral implant, control*) and the direction of shoulder torque (*flexion, extension, adduction, abduction, internal rotation, external rotation*) were fixed factors, and EMG amplitude (*EMG*) was the outcome measure. Random intercepts controlled for subject-specific variability in EMG amplitude in all models. All relevant interactions were assessed.

We utilized the SI to test our hypothesis that the structure of shoulder muscle synergies derived from subpectoral implant breast reconstruction patients would differ from those derived from healthy participants. We first computed the SI between each synergy derived from each subpectoral implant participant to that synergies analog derived from the same side (*dominant, non-dominant*) in every healthy control participant. Descriptive statistics were then used to explore the influence of the experimental group and arm dominance on muscle synergy composition.

Finally, we tested our hypothesis that neuromuscular complexity would be reduced in subpectoral implant breast reconstruction patients using Kruskal-Wallis tests and a linear mixed effects model. Kruskal-Wallis tests examined the influence of group and arm dominance on the number of synergies required to account for more than 95% of the variance in experimental data (N_{95}). Rank sum post hoc tests were used when applicable. The linear mixed effects model examined the influence of arm dominance (*dominant, non-dominant*) and experimental group (*control*, *subpectoral implant*) on the total variance accounted for by first, principal synergy ($tVAF_1$) .

6.4 Results

Fourteen participants who had previously undergone a bilateral mastectomy and subpectoral implant breast reconstruction and ten healthy, age-matched control participants took part in a single experimental session. Subpectoral implant participants were an average of 1,019 days post-reconstruction. T-tests revealed no significant differences between the groups in age ($t_{22}=1.61,\ p = 0.12$), height ($t_{22}=-1.88,\ p = 0.09$), or BMI ($t_{22}=-1.56,\ p = 0.09$). However, subpectoral implant participants were heavier than controls (t_{22}=*-2.11, p = 0.03*). Additional demographic and clinical information can be found in Table 6.1.

Table 6.1 Mean (standard error of the mean) participant demographics for the included experimental groups: healthy controls (Control) and two-stage subpectoral implant (Subpectoral).

	Control	Subpectoral	*t*	*p*
Number of Participants	10	14		
Age (yrs)	55 (2)	49 (3)	1.61	0.12
Height (m)	1.62 (0.02)	1.66 (0.01)	-1.88	0.09
Weight (kg)	62 (2)	73 (4)	-2.11	0.03
BMI (kg/m^2)	24 (0.6)	27 (1.5)	-1.56	0.09
Arm Dominance (L/R)	3/11	1/9		
Days Post-Treatment	-	1019 (83)		
Radiation Therapy	-	2		
Chemotherapy	-	4		
Axillary Lymph Node Dissection (ALND)	-	3		
Sentinel Lymph Node Biopsy (SLNB)	-	7		

Maximal Shoulder Strength

Participants generated maximal shoulder torques in the positive and negative directions of each measurement plane with their dominant and non-dominant arms. Linear mixed effects models assessed the influence of the experimental group, arm dominance, and the interaction between the group and arm dominance for each measure of maximal shoulder strength. All maximal shoulder strength measures were similar with regard to the experimental group (all $F_{1,19} \leq 1.031$, *p=0.323*) and arm dominance (all $F_{1,17} \leq 0.837$, *p=0.373*). Additionally, no group × arm dominance interactions were observed for any shoulder strength measure (all $F_{1,17} \leq 2.86$, $p=0.110$) (Figure 6.2).

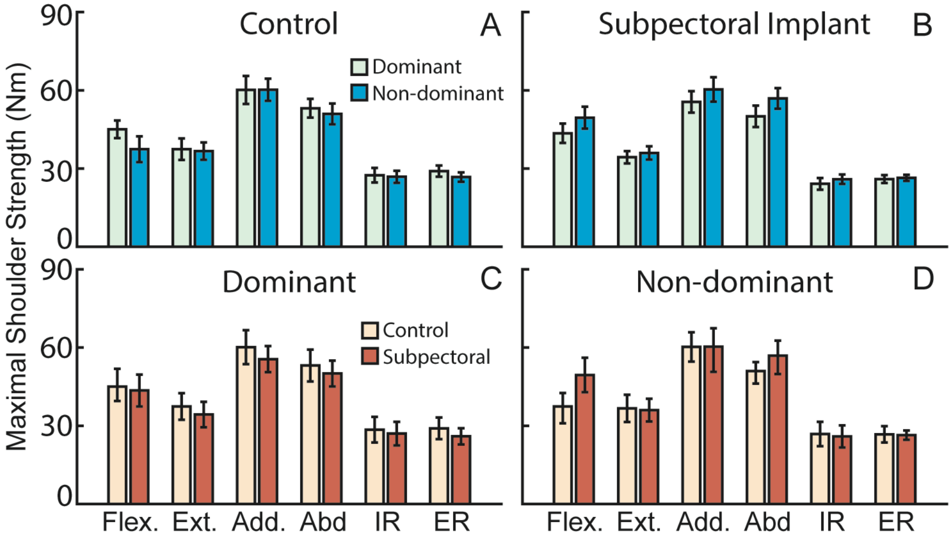

Figure 6.2 Participants generated maximal shoulder torques in shoulder flexion, extension, adduction, abduction, internal rotation and external rotation on their dominant and non-dominant arms. Within each group, arm dominance did not influence shoulder strength (A,B). Strength did not differ between the groups on the dominant (C) or non-dominant (D) arms. Bars represent mean ± standard error.

Shoulder Muscle Activity

Surface EMG recorded activity from 16 upper extremity muscles while participants generated eight three-dimensional shoulder torques in five arm postures bilaterally. We found no main effect of group for any of the included shoulder muscles (all $F_{1,23} \leq 3.70$, $p \geq 0.067$). We observed a main effect of arm dominance in the sternocostal fiber region of the pectoralis major, middle deltoid, upper trapezius, lower trapezius, latissimus dorsi, teres major, infraspinatus, biceps brachii long head, brachioradialis, and triceps brachii lateral head (all $F_{1,1537} \geq 6.81$, $p \leq 0.009$). Muscle activity was greater on the non-dominant arm for the upper trapezius, teres major, and biceps brachii (all $p<0.001$). All other muscles exhibited greater activity on the dominant arm (all $p \leq 0.009$). An experimental group × arm dominance interaction was observed only in the sternocostal fiber region of the pectoralis major and the upper trapezius (both $F_{1,1537} \geq 89.1$, $p < 0.001$) (Figure 6.3). The sternocostal fiber region exhibited greater activity in healthy controls when compared to subpectoral implant participants on the non-dominant arm ($p = 0.017$). The upper trapezius exhibited greater activity in healthy control participants on the dominant arm ($p = 0.002$), and greater activity in subpectoral implant patients on the non-dominant arm ($p = 0.027$)

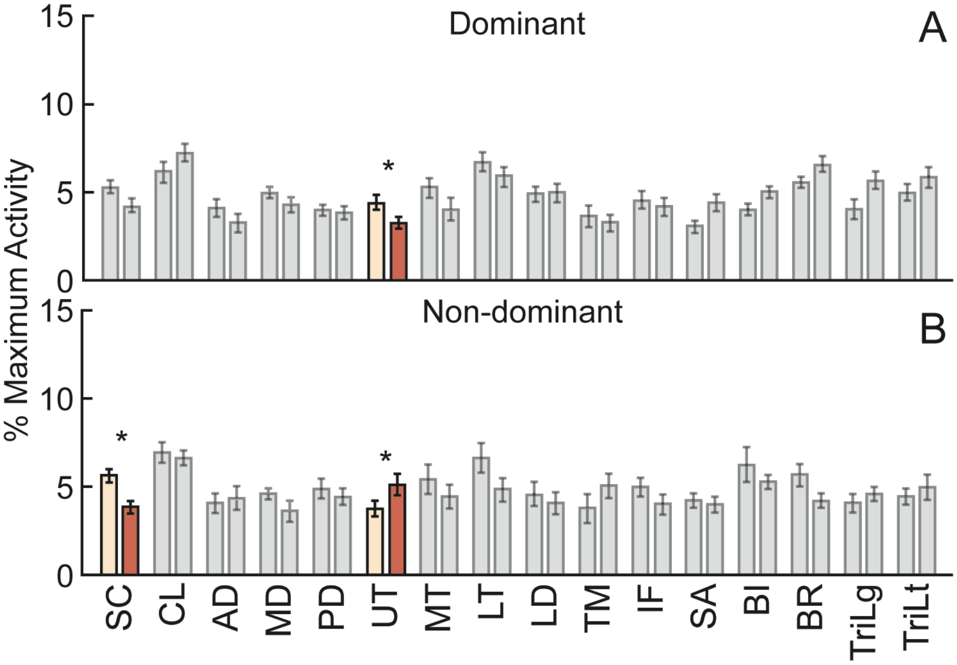

Figure 6.3 Surface electromyography data were obtained from sixteen shoulder muscles while participants generated eight three-dimensional isometric shoulder torques in five two-dimensional arm postures bilaterally. On the dominant arm, only upper trapezius activity differed between the groups (A). On the non-dominant arm, the sternocostal fiber region of the pectoralis major and upper trapezius activity differed between the groups (B). Bars represent mean ± standard error. Significant differences are visualized by colored bars and *.

Subpectoral implant participants and healthy controls activated the shoulder musculature of their dominant arm similarly regardless of the direction of torque generation. No group main effects existed for any muscle (all $F_{1,18} \leq 3.167$, $p \geq 0.092$). Only a single group × elevation torque interaction effect existed ($F_{1,701} = 11.9$, $p = 0.001$): the subpectoral implant group exhibited significantly greater biceps brachii activity during the generation of adduction torques ($p = 0.044$).

Several differences existed on the non-dominant arm. Specifically, a group × plane of elevation torque interaction existed for the middle deltoid and upper trapezius (both $F_{1,805} \geq 6.51, p \leq 0.011$). During the generation of shoulder extension torques, the subpectoral implant group exhibited significantly reduced medial deltoid activity when compared to healthy controls ($p=0.012$). Similarly, the subpectoral implant group exhibited significantly increased upper trapezius activity during the generation of extension torques ($p=0.032$). There was also a group × rotation torque interaction in the brachioradialis ($F_{1,807}=5.76, p=0.017$). The subpectoral implant group exhibited significantly reduced brachioradialis activity during the generation of external rotation torques when compared to the control group ($p=0.027$).

Shoulder Muscle Synergies

Our analysis of muscle synergies described the coordinated activity of shoulder muscles extremely well. Across participants, the derived synergies accounted for 96% (0.7) (mean (SEM)) of the variance in the experimental data. A total of 102 individual synergies were derived across all participants and arms. The number of synergies varied slightly by participant and arm. In general, the derived synergies fell into one of three distinct groups. Synergies derived from representative participants from each experimental group can be found in Figure 6.4. Synergy 1 was characterized by primary contributions from the clavicular and sternocostal fiber regions of the pectoralis major with secondary contributions from the latissimus dorsi and brachioradialis. Synergy 2 was characterized by primary contributions from the medial and posterior deltoids, lower trapezius, and lateral head of the triceps brachii. The third synergy group was characterized primarily by the lower trapezius, with secondary contributions from the middle trapezius, long head of the biceps brachii, and brachioradialis. When averaged across all participants, the overall structure of synergies remains extremely similar but there are slight variations in the weighting of individual muscles (Figure 6.5). Thirty-eight percent of all derived synergies fell into the first group (Synergy 1), 32% fell into the second (Synergy 2), and 30% fell into the third (Synergy 3). All three Synergies were represented equally on the dominant (34/31/35%) and non-dominant (37/33/30%) limbs of healthy controls as well as on the non-dominant arm (40/30/30%) of subpectoral implant patients. However, on the dominant arm of subpectoral implant patients, Synergy 3 accounted for only 21% of all derived synergies.

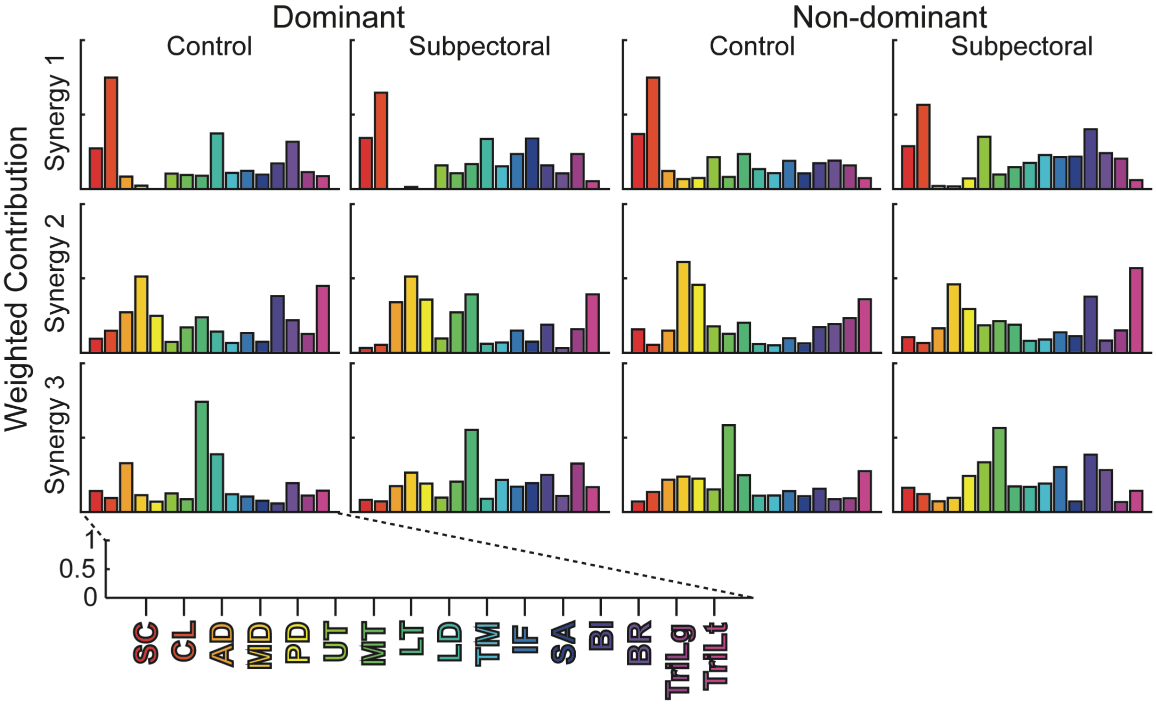

Figure 6.4 Matrix of shoulder muscle synergies derived from representative participants in each of the experimental groups on the dominant and non-dominant arms. Each row represents a separate synergy, while the columns divide participants by the experimental group and arm. The weighted contributions of each muscle to each synergy are represented on a scale from 0 to 1. SC: sternocostal fiber region of pectoralis major, CL: clavicular fiber region of pectoralis major, AD: anterior deltoid, MD: medial deltoid, PD: posterior deltoid, UT: upper trapezius, MT: middle trapezius, LT: lower trapezius, LD: latissimus dorsi, TM: teres major, IF: infraspinatus, SA: serratus anterior, BI: biceps brachii long head, BR: brachioradialis, TriLg: triceps brachii long head, TriLt: triceps brachii lateral head.

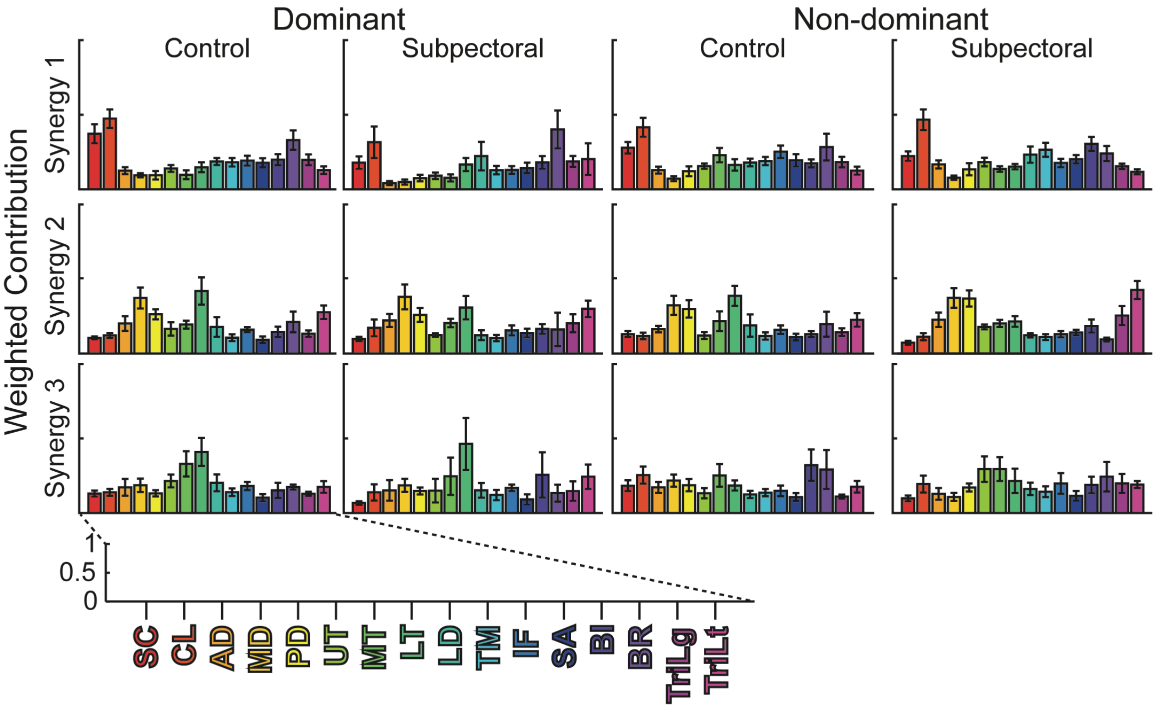

Figure 6.5 Group ± standard error shoulder muscle synergies in each of the experimental groups on the dominant and non-dominant arms. Each row represents a separate synergy, while the columns divide participants by the experimental group and arm. The weighted contributions of each muscle to each synergy are represented on a scale from 0 to 1. SC: sternocostal fiber region of pectoralis major, CL: clavicular fiber region of pectoralis major, AD: anterior deltoid, MD: medial deltoid, PD: posterior deltoid, UT: upper trapezius, MT: middle trapezius, LT: lower trapezius, LD: latissimus dorsi, TM: teres major, IF: infraspinatus, SA: serratus anterior, BI: biceps brachii long head, BR: brachioradialis, TriLg: triceps brachii long head, TriLt: triceps brachii lateral head.

To assess the influence of experimental group and arm dominance on the overall structure of our derived synergies, we computed the SI between the synergies derived from every subpectoral implant participant to their analogs derived from the same side in every healthy control participant. This resulted in a total of 429 similarity indices. Of these, 62% fell above the 0.63 threshold that corresponds to the critical value of Pearson's r at *p=0.01*. When investigating the influence of arm dominance on the synergy structure, we found that only Synergy 2 was more similar than is expected by chance between the groups (mean (SEM) SI: 0.71 (0.02)) on the dominant arm (Figure 6.6). A mean (SEM) SI of 0.62 (0.2) and 0.62 (0.03) was computed for

Synergies 1 and 3, respectively. On the non-dominant arm, Synergies 1 and 2 were more similar than is expected by chance between groups. Synergy 3 derived from the non-dominant arm was not similar between the groups (mean (SEM) SI: 0.57 (0.02)).

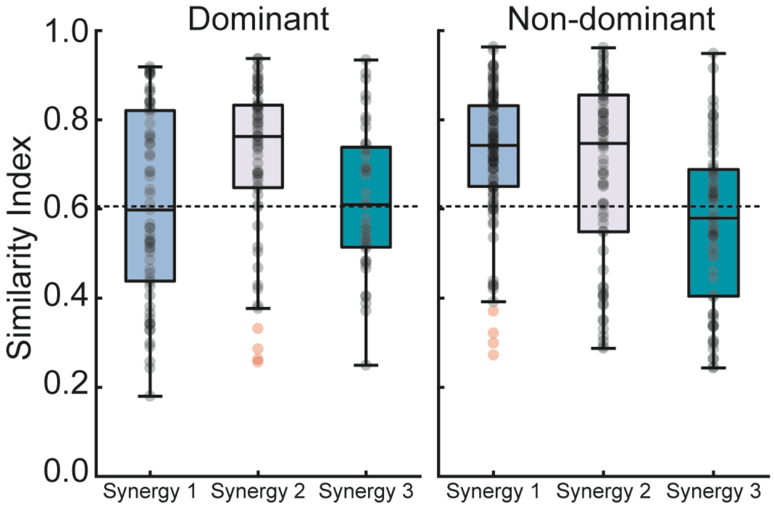

Figure 6.6 Boxplots of the median ± interquartile range similarity index computed between our experimental groups pooled across arms (left), and by arm dominance. Horizontal dashed lines represent the 0.63 cutoff, which was used to determine if two synergies were similar than is expected by chance. Individual data are represented as transparent black dots, while outliers are represented as transparent red dots.

Neuromuscular Complexity

The number of muscle synergies needed to account for 95% of the variance in experimental data (N_{95}), and the variance accounted for by the first, principal synergy (VAF_1) are two measures of neuromuscular complexity. We utilized these metrics in order to examine the neuromuscular impairment associated with subpectoral implant breast reconstruction. We found that N_{95} did not differ by group ($\chi^2_{(1,39)}=1.69$, $p=0.192$), arm dominance ($\chi^2_{(1,39)}=0.581$, $p=0.446$), or by group within hand (both $\chi^2_{(1,189)}\leq 2.48$, $p\geq 0.115$). Similarly we found no effect of group ($F_{1,18} = 0.381$, $p=0.544$) or arm dominance ($F_{1,18} = 0.108$, $p=0.746$) on VAF_1. No interaction between group and arm dominance on VAF_1 was observed ($F_{1,18} = 0.180$, $p=0.677$).

6.5 Discussion

The current study provides the first examination of neuromuscular compensation strategies adopted by breast cancer patients treated bilaterally with mastectomy and subpectoral implant breast reconstruction. We found that shoulder strength is preserved on the dominant and non-dominant arms in bilateral subpectoral implant patients more than 2.5 years post-reconstruction. Additionally, shoulder muscle activity during the generation of three-dimensional shoulder torques was similar between bilateral subpectoral implant patients and healthy controls. We also identified three distinct shoulder muscle synergies underlying three-dimensional shoulder function across five arm postures. The first of these synergies were characterized by contributions from the fiber regions of the pectoralis major, the second consisted of primary contributions from deltoids and lateral head of the triceps brachii, and the third synergy consisted of contributions from the fiber regions of the trapezius. When assessed across dominant and non-dominant arms, the structure of Synergies 1 and 2 was more similar than would be expected by chance between subpectoral implant patients and healthy controls. However, when assessed within each arm, synergies were far less similar between the groups for the dominant arm. Finally, we found that neuromuscular complexity is unaltered by subpectoral implant breast reconstruction, regardless of arm dominance. Together, these findings provide novel insight into neuromuscular adaptions to the most common post-mastectomy breast reconstruction approach. Our results also provide valuable information to drive the development of targeted strategies for the restoration of shoulder function during post-operative care.

Many activities of daily living require the dominant and non-dominant arms to be used separately or in tandem. The successful execution of these activities requires adequate bilateral shoulder strength. Subpectoral implant breast reconstruction requires the surgical disinsertion of the sternocostal fiber region of the pectoralis major. This fiber region is considered a primary contributor to shoulder adduction and internal rotation, and its removal is expected to influence shoulder strength. As such, previous investigations have revealed exhibit significantly reduced shoulder strength in subpectoral implant breast reconstruction patients more than 1 year post-reconstruction[82,152]. However, these findings did not account for arm dominance. In healthy individuals, the dominant shoulder is stronger during flexion or during internal/external rotation[209,210]. Contrary to prior investigations, we found no strength differences between the dominant and non-dominant arms of healthy control participants or bilateral subpectoral implant patients. Our experimental groups exhibited comparable shoulder strength on both the dominant and non-dominant arms. However, this may be a function of the posture in which strength measures were obtained in the current study. Additionally, the bilateral subpectoral implant patients included in the current study had far longer to recover than cohorts included in previous investigations. Nevertheless, our results indicate that the shoulder strength deficits previously observed in bilateral subpectoral implant patients are not present 2.5 years post-reconstruction, and may have been a function of arm dominance.

Clinical practice speculates that the musculoskeletal system compensates for lost function due to muscle disinsertion by recruiting synergist muscles [118,143-145]. The similarity in shoulder strength observed between our experimental groups suggests that bilateral subpectoral implant patients adopt neuromuscular compensation strategies to maintain shoulder strength after the disinsertion of the inferior attachment of the muscle. We identified these compensation strategies using sEMG recordings from 16 shoulder muscles bilaterally during 3-D isometric torque production. Surface EMG data pooled across dominant and non-dominant arms suggest that healthy control participants and bilateral subpectoral implant patients activate shoulder musculature similarly. On the dominant arm, only upper trapezius activity differed between controls and bilateral subpectoral implant patients, with the subpectoral implant patients downregulating its activity. The upper trapezius is responsible for retracting and elevating the scapula [189]. When co-contracted alongside the serratus anterior, the upper trapezius will facilitate elevation at the shoulder joint by upwardly rotating the scapula [189,211,212]. None of these actions are synergistic to the contributions of the sternocostal fiber region of the pectoralis major. Additionally, we observed no related decrease in serratus anterior activity. On the non-dominant arm, bilateral subpectoral implant patients exhibit reduced activity in the sternocostal fiber region of the pectoral major and increased activity in the upper trapezius. Reduced sternocostal fiber region activity is to be expected following its disinsertion. An examination of the influence of planar shoulder torque generation on shoulder muscle activity revealed that group differences in upper trapezius activity on the non-dominant arm were driven by its increased contributions to shoulder extension.

The generation of three-dimensional shoulder torques requires the coordinated contributions of all twenty shoulder muscles. Surface electromyography data alone lacks the nuance necessary to investigate the coordinated activations of shoulder musculature underlying three-dimensional torque generation. We employed muscle synergy analyses to explore the influence of bilateral subpectoral implant breast reconstruction on the coordinated contributions of shoulder musculature. These analyses revealed three muscle synergies describing three-dimensional shoulder function across various two-dimensional arm postures in healthy participants and subpectoral implant patients. The primary contributors to these synergies represent pairs of muscles that generate shoulder or scapular torques in each of the three planes of motions examined in the current study. The middle deltoid (Synergy 2) and the sternocostal fiber region of the pectoralis major (Synergy 1) abduct and adduct the arm, respectively. The clavicular fiber region of the pectoralis major (Synergy 1) assists in shoulder flexion, while its antagonist, the posterior deltoid (Synergy 2) contributes to shoulder extension. The lateral head of the triceps brachii (Synergy 2), biceps brachii (Synergies 1 and 3), and brachioradialis (Synergy 1) primarily actuate the elbow. However, the long head of the triceps brachii and long head of the biceps brachii will externally and internally rotate the shoulder when the position of the elbow remains fixed by muscles such as the brachioradialis [213,214]. Finally, the generation of shoulder joint torques is facilitated by the fiber regions of the trapezius (Synergies 2 and 3), when they co-contract in order to fix the scapula in place [189,211,212].

We found that the overall synergy structure was largely unaffected by subpectoral implant breast reconstruction. Synergies 1 and 2 pooled across the dominant and non-dominant limbs of bilateral subpectoral implant patients were more similar than is expected by chance when compared to healthy controls. However, Synergy 3 pooled across the dominant and non-dominant limbs differed between the groups. The primary contributors to Synergy 3 are the middle and lower trapezius, which actuate the scapula and facilitate torque at the shoulder joint. The lower trapezius is also considered a primary contributor to Synergy 2. This may mean that individuals can forgo the use of a third synergy and still adequately generate shoulder torques by utilizing just Synergies 1 and 2. This is corroborated by our finding that Synergy 3 was present far less frequently than Synergy 2 in bilateral subpectoral implant patients. It is also possible that Synergies 1 and 2 represent the neuromuscular foundation for torque generation at the shoulder, while Synergy 3 represents individual variation. An examination of between-group synergy similarity on the dominant and non-dominant limbs provides greater clarity regarding the influence of bilateral subpectoral implant breast reconstruction on the neuromuscular control of the shoulder. Similar to our findings from synergies pooled across arms, we found that only Synergies 1 and 2 were more similar than is to be expected by chance between the groups on the non-dominant arm. On the dominant arm, however, only Synergy 2 was more similar than is expected by chance between the groups. Synergy 1 is characterized by primary contributions from the fiber regions of the pectoralis major. A reduction in contributions from the sternocostal fiber region of the pectoralis major, which is damaged during subpectoral implant breast reconstruction, is likely driving differences in the structure of Synergy 1 between the groups.

The current study is the first to provide empirical evidence that the neuromuscular system is capable of compensating for the removal of the inferior attachments of the pectoralis major. This was determined by assessing the changes in neuromuscular complexity at the shoulder on the dominant and non-dominant arms. Neuromuscular complexity is reduced following neurological events such as stroke and cerebral palsy but it is unclear how changes in mechanical constraints (the disinsertion of the pectoralis major) influence neuromuscular complexity. We found that bilateral subpectoral implant patients exhibited similar complexity to healthy controls, regardless of arm dominance. Combined with our findings regarding synergy structure, this suggests that bilateral subpectoral implant patients maintain neuromuscular complexity by altering overall muscle synergy structure on their dominant arm, and maintaining synergy structure on their non-dominant. Together, these findings confirm the assumption that the neuromuscular system compensates for the disinsertion of key shoulder muscles.

The current study possessed several limitations. First, muscle fatigue may have influenced our results. In an attempt to minimize fatigue, we assessed shoulder strength in a single posture. Our experimental procedures included forty submaximal torque trials across five arm postures. Shoulder muscle surface electromyography amplitudes are influenced by changes in posture[215-217].

Due to our experimental procedures, it would be extremely challenging to decouple the effects of fatigue from those of changing posture. However, the magnitude of torques produced by participants in the current study is far below what is feasible at the shoulder and should therefore not result in fatigue[218]. A second limitation involved the number of muscles included. We obtained EMG data from only 16 shoulder muscles. Some rotator cuff muscles were omitted because they require intramuscular EMG in order to obtain accurate data [219]. The muscles included in the current study represent primary movers of the shoulder and scapula that can be accurately recorded using sEMG. The accuracy of data obtained from the serratus has been disputed [220]. The results of synergy analyses are entirely dependent on the number of muscles included and including additional shoulder musculature would improve the identification of shoulder muscles synergies[215-217,221]. The presence of skin motion artifact may influence our surface electromyography results. Due to the isometric nature of our experiment, we are confident that skin motion artifact was negligible. The shoulder possesses the largest range of motion of any joint in the human body. However, participants were tested in only five two-dimensional arm postures. This limited number of postures was chosen to reduce fatigue and to represent the center and outside edges of the workspace in which the majority of activities of daily living occur. The arm postures did not include changing the rotation angle or elbow flexion angle. Additionally, we did not account for scapular motion. Assessing a larger number of arm postures would undoubtedly bolster our findings. Finally, shoulder torque magnitude remained constant across postures (34.6% of the lowest MVC) in order to avoid fatigue and to be representative of various occupational tasks[222].

6.6 Conclusions

In conclusion, the current study showed that when controlling for arm dominance, shoulder strength is maintained following subpectoral implant breast reconstruction. The current study also showed that three-dimensional maximal shoulder torque generation is maintained by three shoulder muscle synergies in both healthy and subpectoral implant patients. When compared across the dominant and non-dominant arms, the overall structure of two of these synergies is more similar than is expected by chance between healthy and subpectoral implant patients. However, when assessed within the dominant and non-dominant arms, synergies become less similar only on the dominant arm. We also found that bilateral subpectoral implant patients exhibited similar complexity to healthy controls, regardless of arm dominance. This suggests that bilateral subpectoral implant patients maintain neuromuscular complexity by altering overall muscle synergy structure on their dominant arm, and maintaining synergy structure on their non-dominant. These results provide the first evidence of subpectoral implant patients adopting neuromuscular compensation strategies at the shoulder. These findings provide valuable information for the development of rehabilitation protocols and for the improvement of post-operative care.

Chapter 7. General Discussion and Conclusions

This dissertation addresses several important knowledge gaps regarding the biomechanical, psychosocial, and neuromuscular implications of the most common approaches to post-mastectomy breast reconstruction: 1) what influence does breast reconstruction choice have on the integrity of the shoulder joint and the pectoralis major muscle; 2) do the most common breast reconstruction approaches differentially influence patient-reported well-being; and can objective measures of shoulder biomechanics capture these differences; 3) how does the partial disinsertion of the pectoralis major or the inclusion of radiotherapy affect the pectoralis majors contribution to shoulder function; and 4) what neuromuscular adaptions occur following the disinsertion of the pectoralis major? Results from this dissertation strengthen the surgical decision making process for women undergoing mastectomy and breast reconstruction by systematically assessing the functional deficits caused by the most common post-mastectomy breast reconstruction approaches. Additionally, findings from this dissertation provide a foundational basis for the development of targeted protocols for optimizing the post-operative management of breast reconstruction patients.

7.1 Improving Reconstruction Choice for Breast Cancer Patients

Patient choice is playing an increasingly important role in the management of breast cancer. A growing number of women with early-stage disease are choosing mastectomy over breast conserving therapy[14,183]. Improved genetic testing has resulted in a rising number of at-risk women choosing bilateral mastectomies as a method of prophylaxis[15,20]. Similarly, women diagnosed with unilateral breast cancer are increasingly likely to elect for a prophylactic mastectomy on their contralateral limb[16,17,19,20,193]. Women are often choosing mastectomy over breast conserving therapy, even though both treatments are considered equivalent with regard to disease recurrence and patient survival[17,22-24]. The BRCA1 and BRCA2 genetic mutations are associated with significantly increased breast cancer risk, but they do not guarantee a diagnosis[15]. Patients diagnosed with unilateral breast cancer are also at an increased risk for developing the disease on the contralateral limb, but this only occurs in 2-11% of women[223]. The availability of post-mastectomy breast reconstruction approaches to return the look and feel of healthy breast tissue is an important driving factor for the increase in mastectomy rate[11,25,50]. Breast reconstruction provides women with the ability to control the aesthetic outcome of their mastectomy surgery. The results from this dissertation suggest that patients electing for mastectomy and breast reconstruction should be informed of more than just the aesthetic implications of their decision.

Implications for At-Risk Women Choosing Prophylactic Mastectomy and Breast Reconstruction

Approximately two-thirds of women at-risk for breast cancer opt for prophylactic mastectomy and breast reconstruction patients will choose the subpectoral implant breast reconstruction approach[37]. This reconstructive approach requires the surgical disinsertion of the sternocostal fiber region of the pectoralis major. Previous investigations utilizing patient-reported data suggest the disinsertion of the pectoralis major can alter the underlying integrity of the shoulder joint[81,82,86]. We assessed the implications of choosing subpectoral implant breast reconstruction on shoulder joint integrity using novel, robot-assisted measures of shoulder stiffness. We found that choosing subpectoral implant breast reconstruction leads to significant reductions in shoulder strength. Additionally, our results provide the first evidence that subpectoral implant breast reconstructions fundamentally alter shoulder stiffness. We found that subpectoral implant patients exhibit reduced shoulder stiffness during the generation of shoulder adduction torques when compared to healthy controls, but similar stiffness was observed between the groups at rest. These results provide objective evidence that shoulder joint function is significantly reduced following subpectoral implant breast reconstruction.

The pectoralis major is a primary contributor to shoulder stiffness[93,147,157]. Since common reconstruction procedures disinsert the pectoralis major to place a tissue expander and implant, it is hypothesized that altered pectoralis major function is driving the observed changes in shoulder stiffness. This dissertation included novel assessments of pectoralis major function in breast cancer survivors using ultrasound shear wave elastography. This innovative technique allowed for the material properties of the fiber regions of the pectoralis major to be measured while subpectoral implant patients remained at rest and while they generated shoulder torques. These assessments confirmed that pectoralis major function is fundamentally altered following subpectoral implant breast reconstruction. Specifically, subpectoral implant breast reconstruction patients shift the contributions of the pectoralis major from its disinserted sternocostal fiber region to its still intact clavicular fiber region. These studies provide new evidence that ultrasound shear wave elastography could be a reliable tool for capturing adaptations to the pectoralis major muscle following mastectomy and breast reconstruction.

Together, these findings provide valuable insight for at-risk individuals or women diagnosed with unilateral breast cancer interested in undergoing prophylactic mastectomy and breast reconstruction. Additionally, these findings highlight the need to inform patients of the functional consequences of subpectoral implant breast reconstruction, as patients may experience long-term functional deficits of the shoulder and pectoralis major. Recently, implant-based breast reconstructions have included the placement of the implant pre-pectorally, or above the pectoralis major muscle, which avoids its disinsertion [179,180]. Pre-pectoral implant breast reconstruction surgeries were introduced to address patient complaints of animation deformities that occur when the pectoralis major is disinserted and may have the added benefit of improved functional outcomes. Results from this dissertation suggest that pre-pectoral implant placement should be prioritized when applicable in order to reduce post-operative shoulder morbidity.

Implications for Women Choosing Mastectomy and Breast Reconstruction over Breast Conserving Therapy

Breast-conserving therapy remains the most common approach to the management of breast cancer [224]. The radiotherapy included as part of breast-conserving therapy is associated with increased morbidity of the shoulder[40,113,115,166]. The standard radiotherapy field uses two tangent beams to treat the entire breast. Additional radiotherapy beam(s) can be added to expand the field to include the axilla. In the standard and expanded fields, the pectoralis major receives a large dose of radiation[185]. Radiation damages satellite cells and impairs myoblast proliferation[186,187,225]. These changes reduce the pectoralis major’s ability to remodel, influencing its function[225]. Breast cancer patients choosing between breast-conserving therapy and mastectomy and breast reconstruction should be informed of the unique effects that radiotherapy and breast reconstruction choice have on shoulder and pectoralis major function. We aimed to strengthen patient choice by examining the implications of choosing mastectomy and subpectoral implant breast reconstruction or breast conserving therapy. We found that both subpectoral implant breast reconstruction and breast-conserving therapy significantly reduce shoulder strength when compared to healthy levels but that these groups don’t differ from one another. Furthermore, our results suggest that these strength deficits are driven largely by altered pectoralis major function. The pectoralis major reduces its contributions to shoulder function entirely following radiotherapy, a modality that impacts the entirety of the pectoralis major. On the contrary, subpectoral implant breast reconstruction causes the pectoralis major to shift the contributions of the disinserted sternocostal fiber region to the intact clavicular fiber region. These findings suggest that women choosing between breast conserving therapy and mastectomy and breast reconstruction may be predisposed to shoulder joint and muscle dysfunction regardless of their cancer management. This highlights the need to comprehensively address shoulder morbidity after treatment for breast cancer, as many women do not have the luxury of an innocuous treatment option.

Combined, these results suggest that breast conserving therapy or mastectomy and breast reconstruction will produce altered mechanics of the shoulder joint and pectoralis major muscle. Breast cancer patients will experience long-term and potentially chronic shoulder and pectoralis major morbidity whether they choose a reconstructive technique that requires the disinsertion of shoulder musculature or breast-conserving therapy. The disinsertion of the pectoralis major is often avoided in women undergoing radiotherapy. Results from this dissertation indicate that the disinsertion of the pectoralis major should continue to be avoided in patients previously treated with radiotherapy to avoid undue shoulder and pectoralis major morbidity.

Implications for Women Choosing Between Breast Reconstruction Techniques Following Mastectomy

For women whose breast cancer management requires mastectomy, their breast reconstruction options were traditionally dependent on individual anatomy and the inclusion of radiotherapy. For example, the immediate two-stage subpectoral implant extensively discussed in this dissertation is most commonly used when a patient is not managed with radiotherapy. When radiotherapy is required, a DIEP flap breast reconstruction is better suited for women with a high body mass index, while a latissimus dorsi flap is more common for women with a low body mass index. However, patient preference continues to play a critical role in breast reconstruction choice. Delayed-immediate subpectoral implant breast reconstruction is an option for patients that require post-mastectomy radiotherapy but are interested in subpectoral implant breast reconstruction[226,227]. Immediate DIEP flap breast reconstructions are also used in women undergoing post-mastectomy radiotherapy[228]. We investigated the influence of reconstruction choice on functional shoulder biomechanics in a cohort of patients at least 18 months post-reconstruction. Patients received a combined latissimus dorsi flap with subpectoral implant breast reconstruction, subpectoral implant breast reconstruction only, or a DIEP flap breast reconstruction. We found that patients electing for a combined latissimus dorsi and subpectoral implant breast reconstruction over a DIEP flap could expect a 23.5% decrease in shoulder adduction strength and a 24.6% decrease in shoulder stiffness during the maintenance of adduction torques. When compared to patients undergoing a subpectoral implant breast reconstruction alone, combined latissimus dorsi flap with subpectoral implant patients will exhibit significantly reduced shoulder strength in adduction, abduction, and internal rotation.

Together, these results highlight the important role of the latissimus dorsi and pectoralis major for normal shoulder function and raise concern that their disinsertion likely produces functional deficits in breast cancer survivors undergoing mastectomy and breast reconstruction. The combined latissimus dorsi flap with subpectoral implant breast reconstruction has a greater effect on shoulder strength and stiffness than subpectoral implant breast reconstruction alone or DIEP flap breast reconstruction. For patients choosing mastectomy and breast reconstruction, the results of this dissertation suggest that the combined disinsertion of shoulder musculature should be avoided if possible.

7.2 Improving Post-Operative Care Following Mastectomy and Breast Reconstruction

Advances in breast cancer management have driven a substantial increase in long-term breast cancer survivors nationwide. By 2030, 5 million breast cancer survivors are expected to be living in the United States alone[229]. Shoulder morbidity is a common consequence of many treatments for breast cancer[40,113,166]. Results from this dissertation indicate that the breast reconstruction approach, along with the inclusion of radiotherapy, uniquely influence shoulder strength and stiffness and pectoralis major function for years' post-treatment. Critical steps must be taken to ensure the proper management of post-reconstruction shoulder morbidity to ensure a high post-treatment quality of life. Results from this dissertation provide an objective foundation to optimize the post-operative management of breast reconstruction patients.

Breast reconstruction offers many quality of life benefits over mastectomy alone[30,31,33-35,50,51,148]. Patients undergoing breast reconstruction after mastectomy will self-report improved satisfaction with breasts, sexual well-being, and psychosocial outcomes when compared to patients managed with mastectomy alone [30,31,50,148]. Variations in the approach to breast reconstruction also influence patient-reported quality of life. Patients who have undergone latissimus dorsi flap and subpectoral implant breast reconstruction report lower physical well-being and general satisfaction when compared to DIEP flap breast reconstruction patients[54,149,151]. Latissimus dorsi flap and subpectoral implant breast reconstructions are unique in that they require the disinsertion of shoulder musculature. Results from this dissertation indicate that the functional deficits experienced by subpectoral implant and latissimus dorsi flap breast reconstruction patients last several years post-operatively. Adequate shoulder function is necessary for the execution of activities of daily living, and the inability to perform those activities can influence patient quality of life [230-232]. Therefore, it is reasonable to believe that the differences in quality of life between reconstruction types are driven by their unique effects on shoulder function. However, the connection between objective measures of shoulder function and quality of life is unclear.

Implications for Post-Reconstruction Patient Quality of Life

This dissertation presents the first examination of the causal relationship between objective measures of shoulder function and self-reported quality of life in breast reconstruction patients. Shoulder strength and stiffness, and patient-reported upper extremity pain and function, general physical function, and general psychosocial well-being were obtained from breast reconstruction patients an average of 18 months post-reconstruction. Contrary to previous work, we found that the reconstruction approach did not directly influence patient-reported quality of life. However, we found that multiple measures of shoulder biomechanics were predictive of physical and psychosocial well-being. Specifically, we found that shoulder strength was predictive of upper extremity function, whereas shoulder stiffness was predictive of psychosocial well-being. These results indicate that patient quality of life is most influenced by post-operative shoulder function, rather than breast reconstruction technique or inclusion of radiotherapy. This further highlights the need to properly manage post-operative shoulder function in order to optimize patient quality of life.

The assessment of breast reconstruction patient's shoulder range of motion and strength is frequently performed in a clinical setting by comparing the treated and untreated sides. The outcomes of these assessments are often used as a barometer for a patient's physical well-being. Results from this dissertation suggest that clinical assessments of the shoulder do not provide an accurate appraisal of a patient's ability to perform functional tasks of the upper extremity.

Objective, repeatable measures of shoulder strength and stiffness offer a more reliable method for monitoring a patient's quality of life. Results from this dissertation indicate that shoulder stiffness is predictive of both physical and psychosocial well-being. This is likely due to the nature of shoulder stiffness, which is integral for the initiation and control of movement. However, an excessively stiff shoulder will increase movement difficulty and negatively influence quality of life[164,165]. Results from this dissertation suggest that our novel methods for assessing shoulder stiffness provide enhanced insight into the physical and psychosocial well-being of breast reconstruction patients that cannot be obtained through clinical assessment. They also highlight the important connection between shoulder function and quality of life.

The optimal delivery of breast reconstruction care moving forward should monitor shoulder function. Depending on the institution, the standard of care for a majority of women treated with mastectomy and breast reconstruction likely includes self-directed exercises that focus on the management of pain and lymphedema. Post-operative care is rarely focused on restoring physical function. Fewer than 10% of the breast cancer patients included in this dissertation were prescribed clinician-led physical rehabilitation as a standard of care. Results from this dissertation confirm that if left unmanaged, diminished shoulder function will remain for years post-treatment.

Implications for Post-Reconstruction Compensation Strategies

The pectoralis major is the second-largest shoulder muscle by volume and a primary contributor to shoulder adduction, flexion, and internal rotation[147,157,188]. Findings from this dissertation indicate that many common treatments for breast cancer will influence the force producing capacity of the pectoralis major. Adequate shoulder function requires the combined contributions of all 20 shoulder muscles, including the pectoralis major. Clinicians often assume that remaining intact shoulder musculature will increase their contribution following the disinsertion of the pectoralis major, but it is unclear if this is the case[118]. This dissertation provides the first-ever investigation into the neuromuscular compensation strategies adopted by subpectoral implant breast reconstruction patients more than 2.5 years post-treatment. The dominant and non-dominant arms of patients treated bilaterally with mastectomy and subpectoral implant breast reconstruction, as well as healthy control participants were evaluated. An assessment of bilateral shoulder strength suggests that subpectoral implant patients return to healthy strength levels by 2.5 years post-reconstruction. This supports the hypothesis that in the absence of the pectoralis major, intact muscular increase their contributions to shoulder function. However, a group comparison of EMG amplitudes suggests that this is not the case. The experimental groups did not differ significantly in the contributions of any shoulder musculature capable of compensating for the pectoralis major. The use of EMG amplitudes alone lacks the nuance necessary to examine the coordinated activations of all shoulder muscles, so a novel analysis of the shoulder muscle synergies utilized by subpectoral implant patients and healthy controls on their dominant and non-dominant arms revealed how the disinsertion of the pectoralis major influences shoulder muscle coordination. Findings from this analysis indicate that both subpectoral implant breast reconstruction patients and healthy participants control shoulder torque generation using three distinct muscle synergies. On the non-dominant arm, these synergies are extremely similar between patients and healthy controls. However, on the dominant arm, synergy similarity diminished. Additionally, we found that that bilateral subpectoral implant patients exhibited similar complexity to healthy controls, regardless of arm dominance. These results suggest that bilateral subpectoral implant patients maintain neuromuscular complexity by altering overall muscle synergy structure on their dominant arm while maintaining the overall synergy structure on their non-dominant arm. The findings from this investigation have broad applicability, as it provided the first-ever assessments of post-operative neuromuscular control of the upper extremity in any clinical population. It is also the first to ever comprehensively assess the neuromuscular compensation strategies adopted following the surgical disinsertion of musculature. Finally, it provides novel evidence that the central nervous system adapts to traumatic musculoskeletal damage uniquely on the dominant and non-dominant sides.

Results from this dissertation provide several launching points for improving patient care following mastectomy and breast reconstruction. First, the proper management of shoulder strength and stiffness must be a cornerstone of the post-operative standard of care, alongside the restoration of shoulder internal and external rotation range of motion to optimize the physical and psychosocial quality of life. In particular, shoulder adduction, abduction, internal rotation, and external rotation strength must be addressed regardless of the breast management plan. Additionally, the restoration of shoulder stability in the vertical plane must also be included post-treatment, regardless of the modality. Alongside the already existing data regarding shoulder range of motion, results from this dissertation provide valuable information to form the basis for comprehensive shoulder function rehabilitation following the management of breast cancer. Second, in the absence of proper management of shoulder function, breast reconstruction patients will compensate for the removal of shoulder musculature by adopting unique neuromuscular control strategies. This suggests a focus of treatment must also be placed on restoring 'normal' neuromuscular control of the shoulder, including motor retraining. Currently, there are more than 3.8 million breast cancer survivors living in the United States. Many of which have been living with, and adapted to, long-term functional deficits caused by the management of their cancer. Results from this dissertation provide new evidence of how these patients may adapt, and provide valuable information for clinicians that may eventually treat patients for shoulder morbidity years' post-treatment.

7.3 Limitations

Patients treated with mastectomy and breast reconstruction will exhibit shoulder morbidity and quality of life deficits at different points in their recovery from treatment. In the months immediately proceeding mastectomy, patients will exhibit significantly reduced shoulder strength and will self-report diminished quality of life. Following the completion of breast reconstruction, patients will exhibit deficits in the acute phase of recovery, as well as months and years post-reconstruction. This dissertation is limited in that its findings only pertain to breast cancer patients 1 to 2.5 years post-treatment. We attempted to mitigate this limitation by utilizing well-defined experimental groups with homogenous clinical management plans. Additionally, we obtained experimental data from the dominant and non-dominant limbs when possible. It is still unclear at what point during a patient's recovery when the functional deficits reported in this dissertation appear.

The breast reconstruction techniques examined in this dissertation represent the most popular approaches currently used. However, the latissimus dorsi flap described in this work is far different from the technique most commonly used. Our latissimus dorsi flap participants included the combined disinsertion of the latissimus dorsi and pectoralis major, whereas this technique traditionally involves only the disinsertion of the latissimus dorsi. We attempted to account for this limitation by always comparing our latissimus dorsi flap patients to patients undergoing subpectoral implant breast reconstruction alone. We expect that the deficits caused by the combined disinsertion of the latissimus dorsi and pectoralis major reported in this dissertation are more extreme than those caused by the disinsertion of the latissimus dorsi alone.

Variations within each breast reconstruction technique is largely dependent upon individual anatomy. While the entire latissimus dorsi was disinserted in our combined latissimus dorsi flap with subpectoral implant patients, we were unable to account for the volume of pectoralis major disinserted in any patients. In order to minimize the influence of this limitation, we recruited all breast reconstruction patients from a single surgeon's clinic. In patients undergoing pectoralis major flap reconstruction for head and neck cancer, flap size is significantly correlated with worsening upper extremity disability[75]. It remains unclear how the volume of pectoralis major disinserted during breast reconstruction may influence shoulder function.

Shoulder strength measures were obtained from only a single arm posture. In Chapters 2 through 5, this posture was with the arm flexed 0º and elevated 90º. This posture was chosen to elicit the greatest contributions from the pectoralis major and latissimus dorsi based on their moment arms[147,157]. In Chapter 6, this was with the arm flexed 15º and elevated 75º. This posture was chosen as it loosely represents the center of the normal everyday workspace of the arm[233,234]. A single posture was also utilized in order to avoid fatigue. Shoulder strength is largely a function of arm posture, so this is a significant limitation of this dissertation[209,235]. However, we do not believe this diminishes our findings. The experimental groups in this dissertation were all tested in the same postures. While strength differences between the groups may differ depending on posture, those differences still exist.

With the exception of maximal strength assessments, the shoulder torques generated by participants were submaximal. In Chapters 2 through 5, shoulder torques were scaled to 10% of the maximum value for the given torque direction. In Chapter 6, this magnitude was 34.6%. These torque magnitudes were chosen to ensure the successful performance of experimental tasks. They were also chosen to be representative of shoulder torques generated by everyday occupational tasks[222]. The use of high torque magnitudes would provide added insight to the findings from this dissertation. Finally, our examination of muscle compensation strategies in Chapter 6 only examined subpectoral implant breast reconstruction participants. We believe that other reconstructive techniques involving the disinsertion of shoulder musculature will result in neuromuscular compensation strategies at the shoulder. However, patients treated bilaterally with mastectomy are more likely to choose implant-based breast reconstruction[236].

7.4 Recommendations for Future Research

1) Results from Chapters 2 and 4 indicate that the integrity of the shoulder joint is compromised following post-mastectomy breast reconstruction approaches that require the disinsertion of shoulder musculature. Excessive shoulder joint stiffness reduces patient quality of life and may lead to adhesive capsulitis, which is present in up to 18% of breast cancer patients[164,165]. It would be useful to establish a relationship between objective measures of shoulder joint stiffness and prevalence of adhesive capsulitis in patient populations that include, but are not limited to, patients treated with mastectomy and breast reconstruction.

2) Results from Chapters 2 through 6 suggest that post-mastectomy breast reconstruction approaches that require the disinsertion of shoulder musculature impact shoulder joint and pectoralis major muscle function. Normal *in-vivo* shoulder joint mechanics involve the contributions of all soft tissue articulating the shoulder. Muscle damage, such as in rotator cuff tears, is known to disrupt the glenohumeral joint environment and abnormal glenohumeral

joint mechanics remain even two years after rotator cuff repair surgery[237]. Future work exploring the longitudinal effect of breast reconstruction choice on *in vivo* glenohumeral joint mechanics will better answer how the disinsertion of one or more shoulder muscles impacts the integrity of the shoulder joint complex.

3) Building on suggestion 2, it would be helpful to assess the rate of chronic shoulder sequelae caused by a disrupted glenohumeral joint environment. For example, the pectoralis major and latissimus dorsi assist in maintaining the superior/inferior position of the humeral head in glenohumeral joint capsule [92,238]. Their disinsertion may cause the head of the humerus may shift superiorly, reducing the subacromial space. A similar consequence is observed following a rotator cuff tear[239,240]. Reduced subacromial space may lead to an increased rotator cuff injury rate[241].

4) Most research into the functional implications of mastectomy and breast reconstruction is retrospective and has not explored functional changes in patients after 7.5 years [59]. Results from Chapters 2 through 6 suggest that shoulder and pectoralis major morbidity is potentially chronic following breast reconstruction. Assessing the chronic effects (e.g. > 10 years) of these procedures may better inform the post-reconstruction management of young, at-risk women undergoing prophylactic mastectomy and breast reconstruction.

5) Post-operative physical therapy is playing an increasingly important role in the management of breast cancer survivors. Currently, most physical rehabilitation focuses on managing pain and cancer-related lymphedema. A paucity of research specifically investigating the efficacy

of pre- and post-operative treatment protocols for breast reconstruction patients exists. Results from this dissertation suggest that physical function should be a cornerstone of breast reconstruction patient care. In particular, the restoration of shoulder adduction, abduction, internal rotation, and external rotation strength, and shoulder stability in the vertical plane should be the focus of such care. It would be critically helpful to design and test the efficacy of targeted rehabilitation protocols for the post-operative management of breast reconstruction patients.

Appendix

Table A.1 Results describing the direct effect of breast reconstruction technique on scores from five patient-reported outcome surveys when controlled for each measure of shoulder strength or stiffness (pathway c′). c: constant, Add: adduction, Abd: abduction, Flex: flexion, Ext: extension, IR: internal rotation, ER: external rotation, Rest (V): during rest in the vertical plane, Rest (H) during rest in the horizontal plane.

SPADI

		Strength						Stiffness					
		Add	Abd	Flex	Ext	IR	ER	Rest (V)	Add	Abd	Rest (H)	Flex	Ext
Reconstruction Technique	c	24.1	25.1	22.9	20.5	21.7	26.8	12.6	24.9	26.5	15.5	17.6	20.5
	β	-1.9	-1.9	-3.3	-3.3	-3	-3.1	-3.5	-2.8	-4	-2.7	-2.6	-2.4
	R^2	0.36	0.27	0.32	0.28	0.3	0.37	0.43	0.31	0.39	0.21	0.23	0.29
	p	0.43	0.4	0.13	0.16	0.19	0.16	0.13	0.06	0.08	0.23	0.23	0.28

QuickDASH

Reconstruction Technique	c	15.8	16.5	15.9	13.7	15.3	17.8	5.48	15.2	17	3.08	9.58	11.1
	β	1.4	1.4	0.48	0.51	0.84	0.57	0.35	0.05	-0.38	1.8	1.2	1.3
	R^2	0.19	0.23	0.18	0.08	0.16	0.2	0.36	0.12	0.17	0.24	0.1	0.13
	p	0.53	0.52	0.81	0.81	0.69	0.77	0.86	0.98	0.85	0.36	0.55	0.5

PROMIS

Reconstruction Technique	c	68.5	68.6	69	68.5	64.8	66.1	76.3	71.2	69.6	79.5	75.7	73.7
	β	0.18	0.41	1.2	0.66	0.71	1	1.2	1.5	1.6	-0.26	-0.54	-0.4
	R^2	0.36	0.36	0.31	0.35	0.33	0.39	0.36	0.22	0.26	0.23	0.15	0.24
	p	0.9	0.75	0.35	0.61	0.39	0.41	0.37	0.33	0.24	0.82	0.65	0.72

SF12-PCS

Reconstruction Technique	c	49.7	50.4	53.7	51.4	51.2	49.8	55.8	48.5	47.6	54.8	50.3	49.2
	β	*-0.12*	0.11	0.32	0.28	0.25	0.04	-0.62	-0.37	-0.05	-0.82	-0.7	-0.8
	R^2	*0.04*	0.01	0.21	0.07	0.06	0.02	0.36	0.1	0.13	0.14	0.15	0.19
	p	*0.94*	0.95	0.83	0.86	0.88	0.98	0.68	0.83	0.97	0.59	0.64	0.59

SF12-MVC

Reconstruction Technique	c	42.4	41.6	43.1	46.1	43.9	42.1	53.4	44.1	56.1	60.5	62	66.1
	β	0.65	0.63	1.6	1.8	1.4	1.5	1.5	2.2	-2.5	-0.89	-2.7	-3
	R^2	0.23	0.27	0.2	0.15	0.18	0.2	0.45	0.22	0.22	0.41	0.41	0.48
	p	0.77	0.76	0.43	0.39	0.51	0.44	0.41	0.32	0.21	0.65	0.16	0.11

Table A.2 Results from Sobel tests evaluating the indirect effect of breast reconstruction technique on scores from five patient-reported outcome surveys when mediated by each measure of shoulder strength or stiffness (pathway ai × bk). Add: adduction, Abd: abduction, Flex: flexion, Ext: extension, IR: internal rotation, ER: external rotation, Rest (V): during rest in the vertical plane, Rest (H) during rest in the horizontal plane.

		Strength						Stiffness					
SPADI		Add	Abd	Flex	Ext	IR	ER	Rest (V)	Add	Abd	Rest (H)	Flex	Ext
Reconstruction Technique	β	-1.7	-1.7	-0.32	-0.36	-0.61	-0.55	-0.84	-1.5	-0.28	-0.08	-0.14	-0.41
	z	0.77	0.81	0.72	1.17	1.12	0.82	0.96	1.1	0.48	0.97	0.69	0.74
	p	0.44	0.42	0.47	0.24	0.26	0.41	0.34	0.29	0.63	0.33	0.48	0.46
QuickDASH													
Reconstruction Technique	β	-1.2	-1.2	-0.29	-0.33	-0.65	-0.39	-0.89	-0.59	-0.16	-0.64	-0.02	-0.16
	z	0.62	0.63	0.23	0.25	0.4	0.28	0.18	0.02	0.18	0.81	0.5	0.56
	p	0.54	0.53	0.81	0.81	0.69	0.78	0.86	0.98	0.86	0.42	0.62	0.57
PROMIS													
Reconstruction Technique	β	1.3	1	0.26	0.78	0.73	0.43	0.49	0.23	0.1	-0.39	-0.11	-0.25
	z	0.13	0.31	0.62	0.5	0.53	0.64	0.73	0.93	0.46	0.22	0.41	0.33
	p	0.89	0.75	0.54	0.62	0.6	0.52	0.47	0.35	0.64	0.82	0.68	0.74
SF12-PCS													
Reconstruction Technique	β	0.19	-0.04	-0.25	-0.21	-0.18	0.03	0.67	0.42	0.1	0.29	0.17	0.26
	z	0.07	0.06	0.21	0.18	0.16	0.03	0.4	0.22	0.03	0.52	0.42	0.48
	p	0.94	0.95	0.83	0.86	0.87	0.98	0.69	0.83	0.97	0.61	0.68	0.63
SF12-MVC													
Reconstruction Technique	β	1.1	1.1	0.22	-0.03	0.41	0.26	0.95	0.31	0.04	-1.2	0.64	0.89
	z	0.3	0.3	0.57	0.81	0.63	0.61	0.69	0.94	0.47	0.44	0.73	0.85
	p	0.77	0.76	0.57	0.42	0.53	0.54	0.49	0.35	0.64	0.66	0.46	0.4

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