Massage Therapies – From Lab Bench Top To The Patient

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Miami Marlins Team Physician
Go Fast – Go Alone
Go Far – Go With Others
Outline

1. Evidence for massage-based therapies
2. Animal model of exercise/treatments
3. Mechanical effects of massage
4. Anti-inflammatory effects of massage
5. Massage and muscle regeneration
6. Clinical studies of massage and exercise
7. Next steps
Objectives

1. Apply the concepts of mechanotransduction to explain purported benefits of massage

2. Be familiar with basic science supporting the use of massage therapies

3. Understand the clinical applications of massage and our current evidence-based knowledge for their efficacy
Niccolo Machiavelli, 1469-1527

"There is nothing more difficult to take in hand, more perilous to conduct, or more uncertain in its success, than to take the lead in the introduction of a new order of things."
“I think there is a world market for about five computers.”
Thomas J. Watson
Chairman of IBM, 1943

“There is no reason for any individual to have a computer in their home.”
Ken Olson
President, Digital Equipment Corporation, 1977
1. Massage-Based Therapies - What’s The Evidence?
Clinical Practice

CAUTION

Yes: EBM

In vitro
- Cell/matrix
- Gene
- Biomechanics

In vivo
- Relevant animal models
  - Biology
  - Healing
  - Biomechanics
  - Safety

Controlled Clinical Trials
- Outcomes
- Complications
- Risk / benefit
- Cost / benefit
- VALUE

Study Design:
Cost:

THOUSANDS
TENS OF THOUSANDS
HUNDREDS OF THOUSANDS
1. Massage-Based Therapies – What’s The Evidence Tell Us?

- Moyer CA et al 2009 “The practice of MT is very old, but only in the last 20 years or so has scientific research on MT begun to accumulate.”

Number of documents retrieved, in a year-by-year search using the keyword “massage therapy,” from three Google Scholar database categories. BLE = biology, life sciences, and environmental science; MPV = medicine, pharmacology, and veterinary science; SAH = social sciences, arts, and humanities.

- 37 attendees North American Research Conference
- Modified Delphi approach
1. Massage-Based Therapies – What’s The Evidence Tell Us?

- Established effects
  - Mood, anxiety, low back pain, osteoarthritis, lymphedema, effects of cancer treatment, stress reduction
- Dose-response studies lacking, clearer understanding of mind-body connection, lack of standardization of protocols, biologic mechanisms of action are needed
- What is a valid control in massage studies?
- Value of therapeutic encounter must be examined
- Neuroimaging studies recently employed
- Field T 2014 – fMRI – moderate pressure massage increases activity in the amygdala, hypothalamus, anterior cingulate cortex
1. Massage-Based Therapies – What Are Americans Doing?

• Nahin RL et al. J Pain 2015
• 2007 National Health Interview Survey – 5467 adults and out-of-pocket (OOP) expenditure for arthritis, back pain, fibromyalgia
• $14.9 billion OOP expenses
• $7.5 billion OOP was spent on visits to providers, e.g., chiropractors, acupuncturists
• $5.2 billion OOP was spent for nonvitamin, nonmineral dietary supplements
• $8.7 billion – back pain ($30.7 billion total for LBP)
Manual Therapies And Sports Injuries – Massage

- Mechanical manipulation of body tissues with rhythmical pressure for promoting health and well-being (NCCIH 2006)
- Decreases edema and tissue stiffness, increases blood flow
- Up to 45% of total time in physical therapy for sport-related injury and performance consists of massage treatments (Galloway and Watt, BJSM; 2004)
- 160 million visits annually for relief of musculoskeletal pain and weakness by manipulative or body-based practices
- Challenge = minimal objective evidence it works!
Skeletal Muscle Use/Disuse
2. Eccentric Exercise Model

- Single bout of eccentric exercise (EEX)
  - 7 sets of 10 supramaximal contractions through 55°-155° ankle ROM
- Massage-like loading (MLL) protocol – can vary magnitude, duration, frequency of tissue loading

Methods – Active Property Measurement

- Exercise: bout of damaging eccentric contractions
  - Seven sets of 10 cyclic lengthening contractions
  - Tibiotarsal angle of 95° to 145° of plantarflexion at 150.s-1
  - Muscle activation preceded stretch of the TA muscle-tendon unit by 100 ms (total stimulus train duration = 433 ms)
Methods – Massage Device
Methods – Types of Massage

Wang et al. Annals Biomed Eng 2014
Conceptual Model For Muscle Massage

**Muscle / Joint Function and Structure**
- Peak isometric torque
- Torque joint angle
- Edema, muscle mass, muscle membrane disruption, myofiber damage

**Muscle Regeneration / Repair**
- MGF expression, early repair
- Myotube fusion and differentiation, M-Cad, MyoD, myogenin
- IGF-IEa expression, late repair

**Eccentric exercised-induced muscle weakness, inflammation and damage**

**Immunopathology**
- Inflammatory cytokine expression, inflammatory cell infiltration
- NF-kB expression
- Structural protein degradation (ubiquitin-proteasome pathway)

**AIM 1**
- RO1-AT004922
Essentially all models are wrong, but some are useful. George Box, PhD
3. Mechanical Effects of Massage: Torque-Angle Recovery

Is There A Dose-Response Effect?

One bout of damaging, eccentric contractions and four consecutive days of massage

- Random assignment to one of 8 massage protocols
  - 0.25 or 0.5Hz with compressive force of 5 or 10N for a duration of 15 or 30 min
- Contralateral hind limb as exercised, non-massaged control

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<td>8</td>
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Analysis of Recovery

- Recovery Index (RI): determine the recovery of the mechanical properties due to massage or natural healing

\[ RI = 1 - \left( \frac{\text{pre}_\text{exercise} - \text{final}}{\text{pre}_\text{exercise} - \text{post}_\text{exercise}} \right) \]

- Ratio of final recovery over injury
- RI=0, no recovery; RI=1, complete recovery
Results: Active Properties

0.25Hz, 5N, 30min Condition

0.5Hz, 10N, 15 min Condition
Results: Active Properties

Immediate Vs. Delayed Massage

Effect of Immediate Application of MLL vs. Delayed Application of MLL

- Control
- Immediate
- Delay

RI

* Significant difference
Passive Property Measurement

- Stress relaxation testing
  - Pre-exercise and post-exercise
  - Pre- and post-massage for all four days
  - After four consecutive days of massage

Results - Passive Properties

Change of muscle stiffness

- Instantaneous response fitted using the experimental data
- Curves obtained daily prior to the massage exhibited a monotonic decrease, indicating that the massage actions reduce the elastic modulus (stiffness) of the subject tissue (pre to post-massage)
Immediate vs. Delayed Elastic Response

- Elastic response (muscle stiffness) increased immediately after exercise
- 53% and 41% reduction of stiffness due to immediate and delayed massage, respectively
- No statistically significant recovery from massage estimated by RI
Passive Property Assessment – Tissue Relaxation

- QLV modeled time-dependent responses

Results – Tissue Relaxation
Summary – Massage And Muscle Stiffness/Relaxation

- Tissue stiffness increases with eccentric exercise
- Massage showed greater effects (reduction) in tissue stiffness within day compared with between days
- Massage had little effect on tissue relaxation
- Effects of pain/anesthesia on tissue properties
Transverse (Shear) Forces Associated With Massage

- Previous work - optimal loading parameters focused on compressive force and stroke speed
- Massage results in complex loading of a 3-D tissue
  - Compression, friction, heat
Transverse (Shear) Forces Associated With Massage

![Graph showing shear force over time](image)

- Shear Force (N)
- Time (s)

Longitudinal travel of massage tip
Compressive force
Transverse force
Rabbit TA
Mounting plate for rabbit hindlimb
Summary - Shear Forces Associated With Swedish Massage

- Increased tissue compression = higher shear forces
- Increased massage speed = decreased shear forces
- For given constant compression – shear forces higher with immediate massage
- Shear forces lowest early in massage bout

Which Massage Parameters Best Predict Tissue Recovery?

- Force Magnitude
- Indentation depth
- Stroke length
- Loading duration
- Loading Frequency

Individual contributions

- Work
- Dose
- Power

Combined contributions

Weak Association

Improved Association

Torque RI

QLV RI
\[ P = \int F(t) \cdot v(t) \equiv \bar{F} \ast v \]
Total “Dose” Of Massage vs. Time

\[ \text{Dose} = \int_{0}^{900 s} F(t) dt \]

- Torque RI QLV RI
  - Total Dose: 0.84, 0.39
  - Total Power: 0.86, 0.41
‘The Real Focus of the Affordable Care Act is Wellness’

Kathleen Sebelius
Inflammatory Cells And Tissue Matrix Responses To Injury
Progression Of Injury Or Secondary Damage?

Nikolaou et al ‘87; Faulkner et al ‘91; Best et al ‘99
NSAIDs And Muscle Injury

- Satellite cell activation, proliferation, and differentiation dependent on the COX (COX-1 and COX-2) pathway
- NSAIDs negatively affect satellite cell activation, proliferation, differentiation and fusion (Bondesen BA et al 2006)
NSAIDs And Satellite Cells Following Eccentric Exercise - Humans

- NSAID infusion into VL of one leg following eccentric exercise
- Muscle biopsies before/after 8 days of exercise
- PAX7+ cells to identify satellite cells
- Main finding: suppression of increase in number of satellite cells

Structural Changes Following Injury

4 hr

24 hr
Neutrophil Infiltration And Oxidant Production Following Muscle Injury

**Graph:**
- **X-axis:** Time (h)
  - 4, 24, 48, 72
- **Y-axis:**
  - Oxidant production (pmol/min/mg protein)
  - Neutrophils (cells/mm²)
- Legend:
  - Green: Oxidant production
  - Blue: Neutrophils

**Legend Notes:**
- The graph shows the increase in oxidant production and neutrophils over time post-muscle injury.
Relative Change In Neutrophil Oxidant Generation 24hr Post-Injury

Brickson et al. JAP July 2003
Muscle Structural Changes Following Injury

- IgG treated
- M1/70 treated
Muscle Damage Following Injury

Brickson et al JAP July 2003
Inflammation And Muscle Function

Exercise

Membrane Disruption

Muscle Injury

Massage

Inflammation

2\textsuperscript{nd}ary Injury

Free Radical Production
4. Results – Massage And Muscle Inflammation

Results – Inflammation/Cell Infiltration

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<th>Delayed MLL</th>
<th>Immediate MLL</th>
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<td><img src="image9.png" alt="Image" /></td>
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</table>
Results – Cell Infiltration

- Control - higher number of RPN3/57 & CD11b+ cells compared to immediate MLL (30.9 ± 7.7 vs. 14.4 ± 2.4 and 29.2 ± 9.3 vs. 8.8 ± 2.9, p=0.02 and 0.04 respectively)

- Delayed MLL - higher number of RPN3/57 & CD11b+ cells (16.9 ± 3.0) compared to immediate MLL (41.2± 9.9 vs. 8.8 ± 2.9, p=0.004)

- No difference in RAM11 cell counts
Results – Muscle Wet Weight

- Control (4.01 ± 0.10g) highest
  - Immediate (2.75 ± 0.09g), p=0.03
  - Delayed (3.34 ± 0.15g), p=0.05
- Difference between immediate & delayed MLL (p=.05)
5. Massage And Muscle Regeneration

Mechanical stretching

Cells cultured on flexible substrate

Increased VEGF expression

Massage-like mechanical stretching

Increase VEGF expression, modulate stem cell activity, modulate inflammation, Other?

Enhancing regeneration by stem cell therapy by direct differentiation and indirect paracrine factors such as VEGF (Payne, T. R. et al. 2007; Deasy, B.M et al. 2009; Ota, S. et al. 2011)

Increasing expression of VEGF via exercise (Ambrosio, F. et al. 2010) and possibly mechanotransduction and massage.

Modulating fibrosis by anti-fibrotic agents that neutralize TGFβ-1 (E.g., Foster, W. et al. 3003; Li, Y. et al. 2004; Nigishi, S. et al. 2005) and possibly increasing clearance of TGFβ-1 by massage.
Mechanical Stimulation Increases VGEF Secretion

- **Parameters**
  - Cells stretched at 0.5 Hz, sine wave, 2-D stretch
  - Time points: 1, 4, 10 and 24 hours
  - Measured VEGF expression by ELISA

---

Mechanical stimulation increases VEGF expression in MDSCs

*Beckmann et al, Arterioscler Thromb Vasc Biol. 2013*
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**48 hr delay before massage**

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**24 hr delay**

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**Immediate**

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**Non-massaged**

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**Non-massaged**

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**Evaluate**

Muscle Repair

- Regeneration
- Fibrosis
- Angiogenesis
- Muscle Force
Methods: Immunohistochemical Analysis

- Muscles excised and sectioned into massaged and non-massaged portions
- Five non-overlapping segments counted for percentage of regenerating (centronucleated) fibers
- Sections also evaluated for presence of CD31
- Masson's trichrome staining to detect fibrosis on separate sections.
Results: Regenerating Myofibers

- Centronucleated fibers increased 3.5% in the massaged portion
  - 2.5% in the non-massaged portion
  - 0.7% in contralateral limb
Results: Regenerating Myofibers

- Immediate massage - 128% difference compared to contralateral limb
  - 48 hr delayed massage - 116% difference
  - Injured, non-massaged control had 26% difference
CD31 Yellow
DAPI blue
Results: Angiogenesis

- Massage - 14% increase (normalized to contralateral limb) in CD31+ vessels
  - Immediate massage most effective with 24% increase
## Massage & Muscle Regeneration/Fibrosis

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<th>48 hr delay before massage</th>
<th>24 hr delay before massage</th>
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<tr>
<td>CD31+ blood vessels</td>
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<td>+++</td>
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<tr>
<td>% Regenerating Fibers</td>
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<tr>
<td>Decreased % Fibrotic Area</td>
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Unique Scientific Opportunity

Research taken from the laboratory bench to the park bench to improve human health.
6. Clinical Studies – Massage And Exercise

- Crane et al 2012
  - 11 male recreational runners, bike to exhaustion
  - 1 leg massage oil only, other leg 10 min massage (2 min effleurage, 3 min petrissage, 3 min ‘muscle stripping’, 2 min effleurage)
  - Vastus lateralis biopsy X 2 (2.5 hours apart)
  - Massage activated focal adhesion kinase (FAK), potentiated mitochondrial biogenesis (PGC-1α), and mitigated rise in NFκB
  - ↓ TNF-α, IL-6, and HSP27
Massage and Neuroendocrine/Immune Function

Rapaport et al. 2010

45 mins of Swedish massage vs light touch

Swedish massage (n=29), light touch (n=24)

Oxytocin (OT), arginine-vasopressin (AVP), ACTH, cortisol levels

Massage decreased AVP, small decrease in cortisol, increased number of lymphocytes, decrease pro-inflammatory cytokines (IL-1β, IL-4, IL-6, IL-10), no change in ACTH

Rapaport et al. 2012

5 week study, once or twice weekly

Weekly massage – similar results to 2010 report

Twice weekly massage – increased OT, decreased AVP, decreased cortisol but slight increase in TNF-α, IL-1β, IL-2

"Dosage of massage may result in profoundly different biologic actions"

Leadership and learning are indispensable to each other

JFK
7: Future Work: Blood Flow

- Effects of massage on blood flow
  - Does massage increase local tissue blood flow?
  - Mechanisms?
    - Increased stress on interior vessel walls
      - Release of growth factors
    - Compression/relaxation of vessels?

Chiu JJ and Chien S. *Physiol Rev*, 2011.
Massage And Arterial Blood Flow

- Terason ultrasound doppler system at 4.8MHz
- Transdermal measurements of hindlimb femoral artery blood flow (cm/s) taken pre- and post-massage
Tissue Stress/Strain – Finite Element Modeling

• Magnetic resonance imaging (MRI) of soft tissue
  – Determine *in vivo* anatomical geometry
  – Input 3D geometry into computer model
  – Define material properties using hyperelastic/viscoelastic material definitions
    • Account for tissue relaxation and time-dependent behavior

Methods – Anatomic Muscle Acquisition
Finite Element Modeling – Preliminary Results

• Determine effect of massage at whole muscle level on local internal stress/strain profile
  • Different areas of massaged tissue
  • Distal vs. middle vs. proximal sections
  • Computer modeling of internal stresses and strains
Preliminary Results – Effects of Tissue Friction

Low friction

High friction
Swedish Massage Animal Studies – Summary

- Functional recovery is dose-dependent
- Viscoelastic properties are altered – stiffness > relaxation
  - Changes appear to be greater within massage session compared with between sessions
- What contributes to functional recovery?
  - Compression forces constant (same) between immediate and delayed massage
  - Higher correlation for torque recovery c.f. passive muscle properties
- Our protocol decreases tissue inflammation and edema
- Massage appears to modulate muscle regeneration
Swedish Massage - Summary
When you come to a fork in the road, take it.

Yogi Berra
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<th>Details</th>
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Thank-you