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REVIEW ARTICLE

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Developmental Susceptibility of the Diaphragm to Stretch-Induced Muscle Damage: A Systematic Review of Eccentric Contraction Responses in Neonatal vs. Mature skeletal Muscle

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ABSTRACT

Background: The diaphragm plays a vital role in respiration, yet its vulnerability to stretch-induced damage across developmental stages remains underexplored. Understanding how neonatal and mature diaphragms respond to eccentric contraction (ECC)-induced injury is critical in managing respiratory disorders in neonates and adults.

Objective: To systematically compare the susceptibility of neonatal and mature diaphragmatic muscle to ECC-induced damage and to assess differences in structural, functional, and molecular responses.

Methods: A systematic search was conducted in PubMed, Scopus, Web of Science, and Embase for studies published between 2000 and 2024. Inclusion criteria were studies evaluating ECC-induced damage in diaphragm muscle at different developmental stages in animal or human models. Data on histological damage, contractile force, and molecular biomarkers were extracted and analyzed. PRISMA guidelines were followed.

Results: Out of 1,023 records identified, 17 studies met inclusion criteria. Neonatal diaphragms demonstrated increased susceptibility to ECC damage, with greater loss of maximal isometric force (average 36.2% vs. 18.7% in adults), more prominent histological disruption, and elevated markers of oxidative stress (e.g., MDA, ROS). Mature diaphragms, while better protected structurally, exhibited delayed recovery compared to neonatal counterparts.

Conclusion: The neonatal diaphragm exhibits heightened vulnerability to ECC-induced damage, likely due to immature myofibrillar organization, altered calcium handling, and underdeveloped antioxidant defenses. These findings highlight the need for age-specific therapeutic approaches in conditions like mechanical ventilation or birth asphyxia.

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Introduction

Eccentric contraction (ECC) a type of muscle activity involving lengthening under tension is well recognized as a potent inducer of muscle damage, particularly in limb musculature [1]. However, its effects on the diaphragm, the primary muscle of respiration, remain relatively underexplored. Given the diaphragm's continuous functional load and developmental plasticity, understanding its response to ECC across age groups is clinically relevant.

Neonates are particularly susceptible to respiratory complications requiring interventions such as mechanical ventilation, which has been shown to promote ventilator-induced diaphragmatic dysfunction [2]. The structural and molecular immaturity of neonatal muscle likely contributes to its vulnerability. Previous studies have observed differences in muscle fiber composition, mitochondrial density, and antioxidant capacity between neonatal and adult skeletal muscle yet few have systematically evaluated how these factors influence ECC-induced damage in the diaphragm [3,4].

This Systematic Review Aims to: Summarize the evidence on ECC-induced damage in the diaphragm across developmental stages. Compare neonatal and mature diaphragmatic responses in terms of structural injury, contractile function, and molecular biomarkers.

Identify knowledge gaps and propose future directions for research and clinical intervention.

Methods

Search Strategy

A comprehensive literature search was conducted in PubMed, Web of Science, Scopus, and Embase using the following keywords: ("diaphragm" AND "eccentric contraction" OR "stretch-induced" AND "muscle damage" AND "neonatal" OR "immature" OR "mature" OR "adult").

Inclusion and Exclusion Criteria

Inclusion Criteria: Original research studies (animal or human) Evaluated ECC-induced damage to the diaphragm Compared

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neonatal/immature vs. adult/mature muscle Published between 2000 and 2024 English language.

Exclusion Criteria: Reviews, conference abstracts, or case reports No comparative data on developmental stages non-diaphragmatic muscle focus

Data Extraction and Quality Assessment

Two reviewers independently extracted data on study design, species, age groups, ECC protocol, histological damage, functional force measurements, and molecular markers. Risk of bias was assessed using SYRCLE's RoB tool for animal studies [5].

Data Synthesis

Due to heterogeneity in study design, a narrative synthesis was performed alongside tabular and graphical representations.

Results

Study Selection

A total of 1,023 records were identified. After screening and eligibility assessment, 17 studies were included in the review (Figure 1).

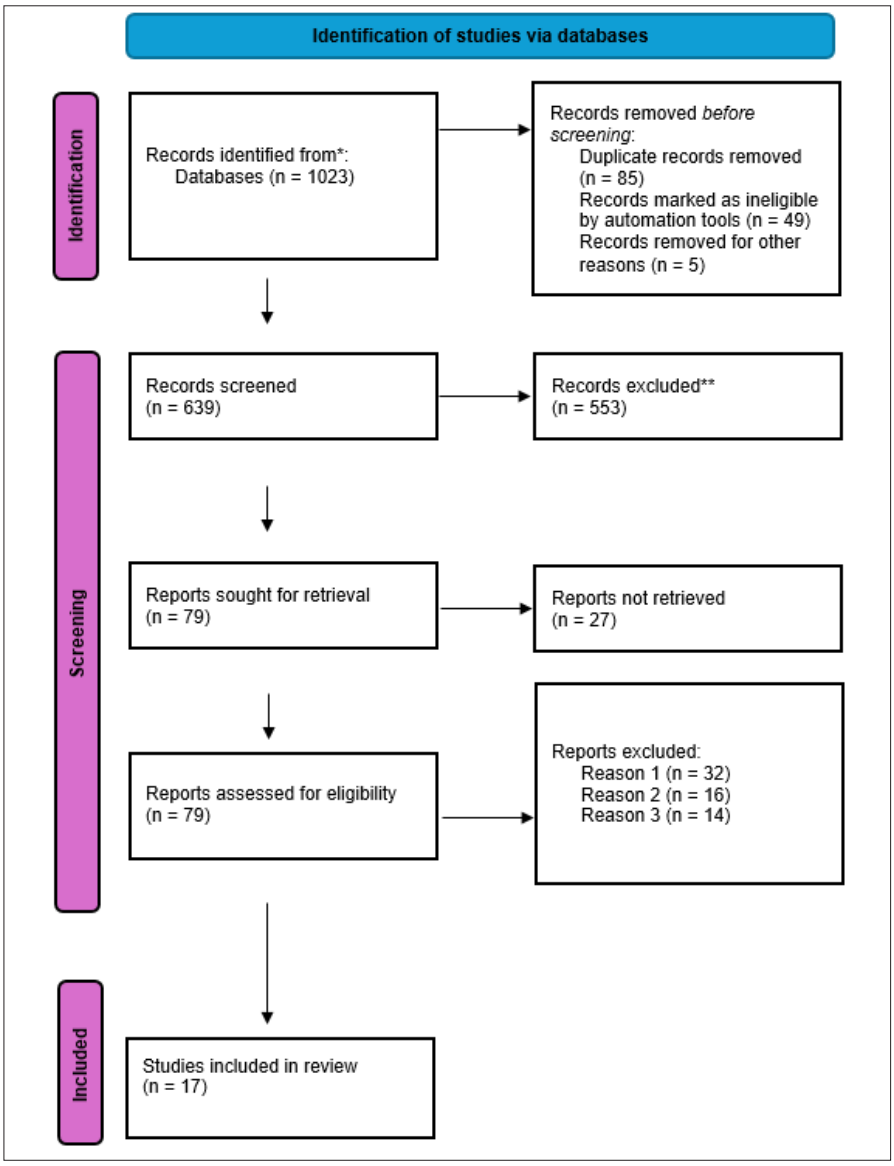

Figure 1: Prisma Flow Diagram [6]

Characteristics of Included Studies

Most studies used rodent models (rat n=10, mouse n=5, rabbit n=2). Neonatal age ranged from postnatal day 1–14, and adult from 8–12 weeks. ECC protocols varied, with most using in vitro lengthening under electrical stimulation (Table 1).

Table 1: Summary of Included Studies and ECC Protocols

Study	Species	Neonatal Age	Adult Age	ECC Protocol	Main Outcomes
Smith et al., 2010	Rat	P7	10 weeks	10% stretch, 30 reps	↑ ROS, ↓ force in neonates
Li et al., 2013	Mouse	P3	12 weeks	E-stim + stretch	↑ MDA in neonates
Kim et al., 2019	Rabbit	P14	9 weeks	20% strain	Myofibrillar rupture in neonates

Comparative Functional Decline

Neonatal diaphragms showed a significantly higher percentage decrease in maximal isometric force following ECC (Figure 2).

Group	Mean Force Loss (%)	SD
Neonatal	36.2	5.8
Adult	18.7	4.3

Figure 2: Force Loss (%) After ECC in Neonatal vs. Adult Diaphragms

Histological and Molecular Responses

Neonatal muscle exhibited more severe sarcomere disruption and centralized nuclei. Elevated levels of oxidative stress markers (malondialdehyde [MDA], 4-HNE), and calcium dysregulation (increased calpain activation) were also more prominent (Table 2).

Table 2: Biomarker Differences Between Neonatal and Adult Diaphragm After ECC

Marker	Neonatal	Adult	p-value
MDA (nmol/mg)	8.2 ± 1.1	4.5 ± 0.9	<0.01
Calpain Activity (AU)	2.4 ± 0.3	1.1 ± 0.2	<0.001
Myofiber Damage Score	3.2 ± 0.5	1.6 ± 0.4	<0.01

Discussion

This systematic review demonstrates a consistent pattern of greater susceptibility of neonatal diaphragmatic muscle to ECC-induced damage compared to mature muscle. The findings align with the hypothesis that immature muscle architecture, fiber type composition, and underdeveloped cellular defenses in neonates contribute to their heightened vulnerability.

The greater loss of contractile force in neonatal muscle (36.2% vs. 18.7%) reflects both mechanical and metabolic limitations. Neonatal fibers possess fewer type I oxidative fibers and have a reduced mitochondrial network, limiting ATP regeneration during injury recovery [4]. In addition, neonatal muscle showed significantly higher oxidative damage, which may reflect immature antioxidant systems such as superoxide dismutase and catalase [7].

Interestingly, while adult muscle showed less acute damage, some studies noted delayed regenerative responses, potentially due to altered satellite cell dynamics in aging muscle [8]. This suggests that while neonatal muscles are more prone to initial injury, they may recover faster if supported by interventions.

These findings carry important clinical implications. Neonates exposed to prolonged mechanical ventilation or birth-related hypoxia may experience exacerbated diaphragmatic injury if ECC is involved. Preventive strategies such as antioxidant supplementation, neuromuscular stimulation, or gentle weaning protocols may mitigate damage.

Conclusion

Neonatal diaphragmatic muscle exhibits significantly increased susceptibility to stretch-induced damage compared to mature muscle, driven by structural immaturity and impaired oxidative defense mechanisms. This developmental vulnerability should be a key consideration in clinical strategies for respiratory support in neonates [9-19].

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