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*DOI 10.21661/r-559828*

# MECHANOTHERAPEUTIC APPROACHES TO MANIPULATE SPERM INDICES: NOVEL ULTRASONIC METHODS FOR TREATING ASTHENOSPERMIA AND POTENTIALS FOR MALE CONTRACEPTION

***Abstract****: the article deals with the fact that sperm motility is a significant predictor of male fertility potential and is directly linked to fertilization success in both natural and some forms of assisted reproduction.*

***Keywords****: acoustic-based mechanotherapy, sperm motility, male contraceptive.*

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# МЕХАНОТЕРАПЕВТИЧЕСКИЕ ПОДХОДЫ К МАНИПУЛИРОВАНИЮ ПОКАЗАТЕЛЯМИ СПЕРМЫ: НОВЫЕ УЛЬТРАЗВУКОВЫЕ МЕТОДЫ ЛЕЧЕНИЯ БЕСПЛОДИЯ И ВОЗМОЖНОСТИ МУЖСКОЙ КОНТРАЦЕПЦИИ

***Аннотация****: в статье речь идёт о том, что подвижность сперматозоидов является важным предсказателем потенциала мужской фертильности и*

*напрямую связана с успехом оплодотворения как в естественной, так и в некоторых формах вспомогательной репродукции.*

***Ключевые слова**: акустическая механотерапия, подвижность сперматозоидов, мужская контрацепция.*

1. *Introduction*

Sperm motility can be impaired by both genetic and environmental factors. Cells exposed to high frequency ultrasound demonstrate a higher rate of metabolic activity, producing more energy required for swimming, and its ability to swim faster by beating at higher frequencies and with larger amplitudes.

On the other hand, if the exposure is too prolonged it may have a negative effect. The deleterious nature of over exposure could potentially be due to the induced mechanical stresses. Excessive stresses cause increased mitochondrial membrane permeability and interrupted ATP production and thus compromised sperm motility. In this paper we will review the existing acoustic-based methods using different ultrasonic frequencies under controlled conditions of power and exposure time and their potentials for manipulating sperm indices and spermatogenesis leading to either treating asthenospermia developing another safe, efficient and inexpensive method for contraception that would only help to lower the rate of unwanted pregnancies and abortions.

This single cell level mechanotherapy approach provides a new opportunity to boost sperm motility in assisted reproduction, particularly for samples that suffer from poor sperm motility, hence improving the outcome of assisted reproductive technology.

A permanent or reversible method of contraception based on therapeutic ultrasound treatment emerging from that could also encourage more men to share greater responsibility for family planning.

Infertility is a rising global health issue that impacts over 70 million couples per year [1]. Male factor infertility accounts for 50% of infertility cases, primarily mediated by deficits in sperm number and/or function [2–4]. Sperm motility plays a central role in both natural fertilization and clinical sperm selection as the key parameter reflecting the fertility potential of individual sperm [5, 6]. In natural reproduction, sperm must

traverse a complex route from the seminal fluid to the viscous fluids contained within the cervix, uterus, the fallopian tube, and ultimately through the highly folded and complex lumens within the tube to achieve fertilization [7, 8]. However, sperm motility can be impaired through factors attributed to the modern lifestyle, such as pollution and unhealthy diets, [1] or through endogenous genetic factors [9]. To circumvent infertility problems, assisted reproductive technologies (ART) have been developed [10].

There is an absence of noninvasive, drug-free methods, to restore or enhance sperm motility without introducing potential damage to their viability or DNA integrity.

2. *Sperm Energy and synthesis of Motility*:

In humans, the sperm tail or flagella is ≈60 μm in length and is composed of a relatively rigid midpiece which contains the mitochondria, attached to a more flexible principal piece and at the extremity an end piece wherein the axoneme, the driveshaft of the sperm tail, is surrounded solely by the plasma membrane [11]. A sperm's energy for normal cellular function and motility is mainly synthesized via two distinct mechanisms, through glycolysis, which occurs in the head and the principal piece of flagellum, and in the mitochondria through an oxidative phosphorylation process. In both of the processes, adenosine triphosphate (ATP) is produced and used to drive the ATP-activated dynein motors within the axoneme [12].

The ATP-activated dynein arms sequentially slide one of the nine outer microtubules in the 9+2 axoneme structure over the neighboring doublet to generate the flagellar waveform, where dynein-tubulin binding affinity is regulated by long-residence ATP binding site [13]. Changes in sperm motility are likely linked to an increased mitochondrial respiration as observed in several species during capacitation and hyperactivation [14]. Indeed, during a sperm's metabolic process, up to 2% of the intracellular oxygen (O2) is converted into superoxide radicals ($O2^{-}$) followed by the production of hydrogen peroxide (H2O2) and hydroxyl radicals ($OH^{-}$), both types of reactive oxygen species (ROS) [14]. ROS molecules are required for sperm capacitation [15], the acrosome reaction [16] and sperm-oocyte binding,[16] which in turn are required for fertilization oxidative damage that influence sperm motility [17, 18].

3. *Acoustic–based Mechanotherapy*

By studying the relationships between sperm velocity and acoustic parameters, Tsuruta et al. (2012) proved that acoustic-based methods significantly improve the motility characteristics of sperm by 30% after a brief 20s acoustic exposure at a frequency of 19.28 MHz and power of 2 W as shown on *Figure 1*. Compared with current clinical methods to increase sperm motility, this high-frequency acoustic-based method is biocompatible, without any adverse effects on either sperm viability or DNA integrity. Moreover, ultrasound has been utilized prevalently in different medical applications including diagnostics, therapy, and surgery, [19] without noticeable side-effect, which indicates the noninvasiveness of this approach. Cells exposed to high frequency ultrasound demonstrate a higher rate of metabolic activity, producing more energy required for swimming, and its ability to swim faster by beating at higher frequencies and with larger amplitudes. This single cell level mechanotherapy approach provides a new opportunity to boost sperm motility in assisted reproduction, particularly for samples that suffer from poor sperm motility, hence improving the outcome of assisted reproductive technology.

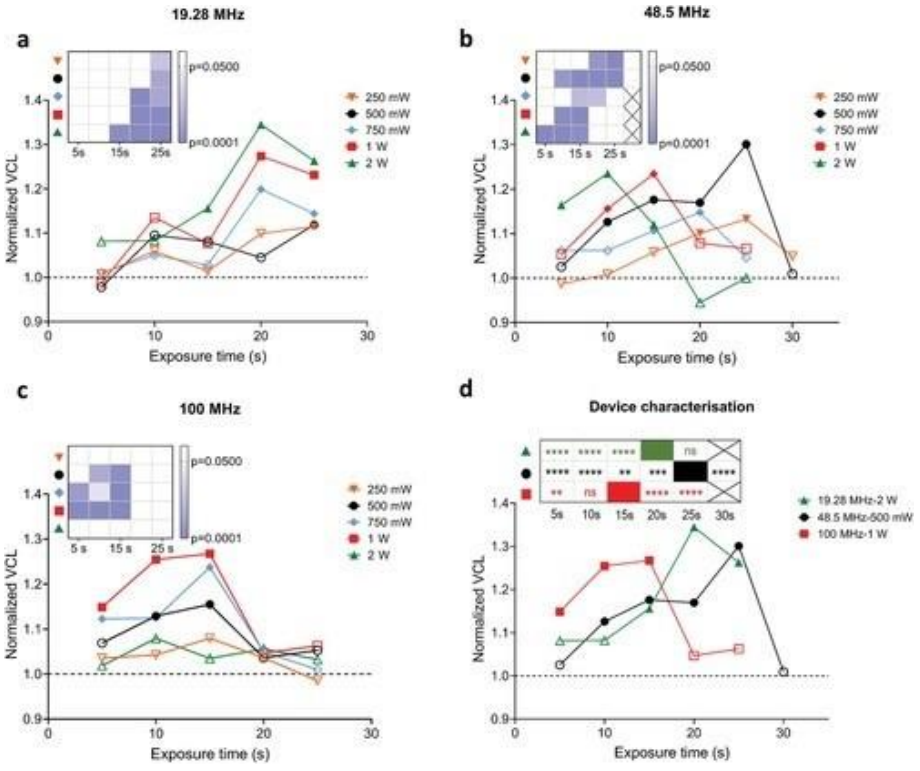


*Fig. 1.* Increase in sperm curvilinear velocity (VCL) post-exposure to ultrasound [61]

*Metabolism*

This increase in metabolism and sperm motility post ultrasonic exposure might be attributed to effects on cell signaling pathways. An influx of Na+, H+, Ca2+ and/or HCO3 – can cause an increase in sperm motility, via the activation of ion channels [20].

Effect of power and exposure time at an SAW frequency of:

a) 19.28 MHz;

b) 48.5 MHz;

c) 100 MHz on the group-mean centered VCL post-exposure;

d) relative resultant normalized post-exposure VCL as a function of exposure time when excited at frequencies of 19.28, 48.5, and 100 MHz (at optimum excitation powers).

*Conventional Methods Vs Ultrasound*

In comparison with conventional methods, ultrasound offers both noninvasiveness and time efficiency, considering the achieved improvement of ≈30% in both curvilinear velocity and the number of motile sperm after 20s acoustic exposure and without any adverse effects on sperm DNA integrity. It is noteworthy that traditional semen preparation methods (swim up and density gradient centrifugation) cause a comparable improvement in sperm motility (≈30%improvement), [ 21, 22] but by removing a subpopulation of immotile sperm. In comparison, our method offers a fundamental advantage, as we increase the swimming velocity and subsequently the motility of *the same* population of cells by exposing them to ultrasound, without the necessity for any preprocessing or selection. This improvement in sperm motility, in the absence of any chemical treatment and/or selection, provides new opportunities for selecting motile and viable sperm in clinics, to be used for the fertilization cycles either directly or after inducing sperm hypermotility using conventional clinical methods [23].

Moreover, these findings also provides new insight for altering the metabolism level of other micro swimmers, such as *E. coli*, for applications relevant to environmental monitoring [24] and protein production [25].

*What if the exposure is too prolonged*?

the exposure is too prolonged it may have a negative effect. The deleterious nature of over exposure could potentially be due to the induced mechanical stresses. Excessive

stresses cause increased mitochondrial membrane permeability and interrupted ATP production [25] and thus compromised sperm motility [27]. Moreover, prolonged mechanical stimulation has been shown to increase membrane stiffness in adherent cells [28] and reduce membrane fluidity and increase cell rigidity has been shown to contribute to reduced sperm motility levels under other conditions [29].

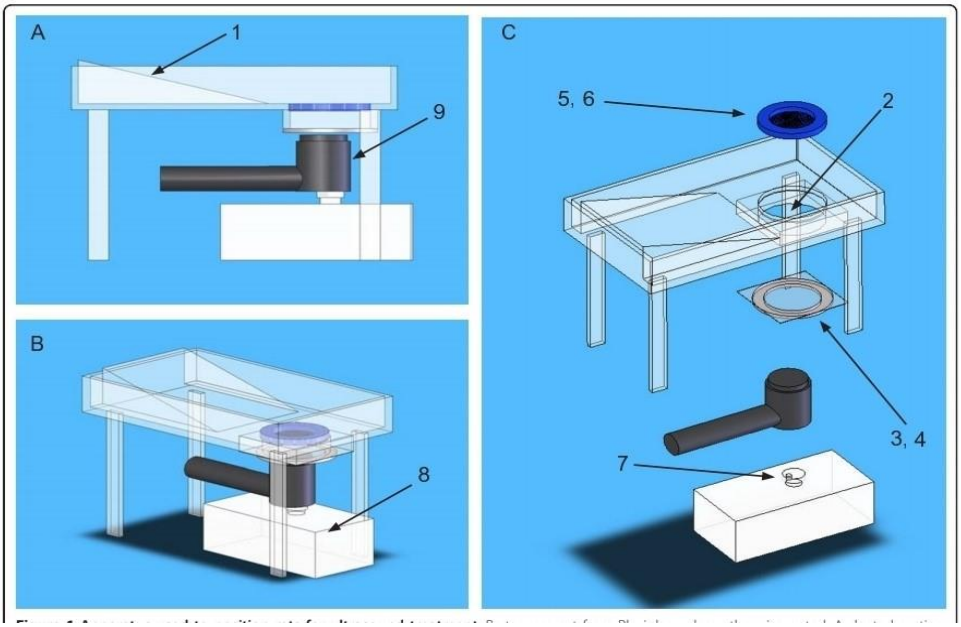


*Fig. 2.* Apparatus used to position rats for ultrasound treatment

Parts were cut from Plexiglas unless otherwise noted [60].

A slanted section supported most of the rat's body is placed above the level reached by re-circulating coupling medium. The scrotum of the rat is placed within the ultrasound treatment chamber after using some kind of ligature to retain the testes within the scrotum (not shown).

*Ultrasound and Male contraception*

We found that 3 MHz ultrasound delivered with 2.2 Watt per square cm power for fifteen minutes was necessary to deplete spermatocytes and spermatids from the testis and that this treatment significantly reduced epididymal sperm reserves. 3 MHz ultrasound treatment reduced total epididymal sperm count 10-fold lower than the wet-heat control and decreased motile sperm counts 1,000-fold lower than wet-heat alone. We found that germ cell depletion was most uniform and effective when we rotated the therapeutic transducer

to mitigate non-uniformity of the beam field. The lowest sperm count was achieved when the coupling medium (3% saline) was held at 37 degrees C and two consecutive 15-minute treatments of 3 MHz ultrasound at 2.2 Watt per square cm were separated by 2 days.

*Effects*

A series of publications, it was shown that a single application of ultrasound could result in a dramatic loss of germ cells from testes and that this loss of germ cells was reversible. No notable side effects other than infertility were reported during studies with rats, dogs and monkeys [30]. This method was tested on several human subjects who were already scheduled for orchiectomy to treat prostate cancer. These men reported that the procedure was pain-free, only creating a gentle feeling of warmth [30, 31].

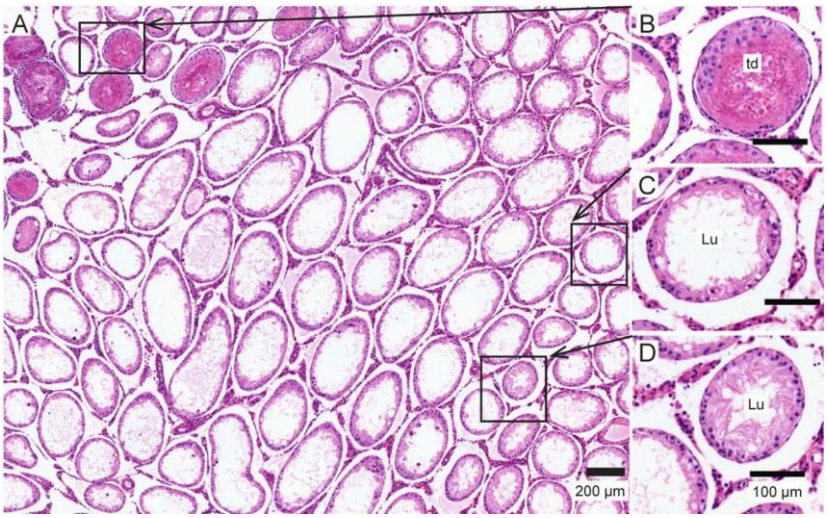


*Fig. 3.* Testis histology two weeks after 3 MHz ultrasound (Group 4)

A. A more complete loss of spermatogenic cells after the wet heat treatment resulting in a shorter epithelium and a larger diameter lumen.

B. An isolated cluster of tubules in this particular animal showed evidence of thermal damage (td) in addition to the loss of spermatogenic cells.

C. Most tubules had a very short epithelial layer and increased lumen diameter due to the loss of all spermatocytes and spermatids.

D. Tubules with a larger epithelial layer and smaller diameter lumen were still missing spermatocytes and spermatids.

*Potential applications*:

Depleting spermatocytes and spermatids from testes noninvasively with therapeutic ultrasound have multiple applications [60].

1) creating testes depleted of differentiated spermatogenic or meiotic cells, investigators could test directly the effect of compounds proposed to regulate spermatogonia which cells are assayed by colony formation after transplantation into recipient testes depleted of germ cells by chemical tremendous [32–34];

2) controlling various domestic pet populations could be developed. Researchers [35] have successfully used therapeutic ultrasound as a non-invasive method for canine sterilization and will not affect testosterone production by Leydig cells [30];

3) ultrasound treatment could be adopted as part of a larger strategy to control nuisance animal populations using the trap-neuter-return model [36, 37]. Introducing sterile males into a population was effective in controlling insect populations [38–42]. Controlling deer populations in urban or suburban areas would accrue many public health benefits since white-tailed deer carry ticks that transmit disease [43–44], are at risk for tuberculosis and will reduce automobile accidents [45–49];

4) addressing the global health issue of unintended pregnancies as reported by WHO [50–52]. Yearly these unintended pregnancies result in almost 50 million abortions; almost half of which are classed as unsafe, resulting in 47 thousand maternal deaths [53, 54]. In the United States alone there are at least 3 million unintended pregnancies each year representing about 50% of all pregnancies [55, 56].

*Conclusion*

Noninvasive approaches to boost sperm motility utilizing the concept of acoustic based mechanotherapy, offer promising opportunities to manage the male infertility issue by using ultrasound to induce sperm motility and therefore detect viable sperm for ICSI [61].

The chances of pregnancy decrease linearly when sperm concentrations are below 40 million sperm/ml [57] and contraception considered effective contraception is when sperm concentration to fall below 3 million sperm/ml which could be achieved by means of therapeutic.

However, further studies must be conducted to verify that it causes no detrimental, long-term effects [60].

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