

Non-invasive delivery of radiofrequency energy in women with faecal incontinence, the new era. The new-generation DQRF™ device

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Abstract

Introduction: With at least one humiliating episode per month, faecal incontinence, variable from undergarment soiling to urge and passive incontinence, is a vexing problem for no less than one adult woman out of ten. The efficacy and impact on the quality of life of temperature/movement-controlled radiofrequency energy delivery to the sphincter complex with invasive needles are actual but rapidly wane. An innovative device is a candidate to overcome previous radiofrequency technologies' limitations and discomfort in faecal incontinence. It is equipped with an anatomical probe and the non-invasive Dynamic Quadripolar RadioFrequency™ technology and exploits the in-depth penetration of active principles via Ultra-Pulsed Radioporation™. A careful study of the anatomically and functionally delicate anal sphincter complex was the basis for the device design.

Methods: Explorative cohort study in 25 unselected ambulatory women 30 to 71 years old, nulliparous to multiparous, with medium-severity faecal incontinence and quality of life disruption. Wexner score assessment before the first session and at the end of the radiofrequency treatment cycle; further follow-up control after about one more month.

Results: At the end of the treatment cycle (5.8 ± 0.91 mean sessions; median, 6.0), Wexner scores (overall baseline mean, 8.6 ± 2.65 ; overall final mean, 0.4 ± 0.58) decreased to zero in fifteen women with occasional solid, liquid and gas incontinence in one, five and four women, respectively, all under control at the final follow-up visit, with no immediate or later side effects and total compliance.

Conclusions: The non-invasive device effectiveness in daily life was satisfactory. The benefit of eliminating invasiveness in radiofrequency energy delivery needs confirmation in well-designed incontinence studies, yet it already looks like a definite plus.

Abbreviations: CCF-FI[®] Cleveland Clinic Florida Faecal Incontinence (score); DQRF™: Dynamic Quadripolar RadioFrequency™; FI: Faecal incontinence; FIQLS: Faecal Incontinence-related Quality of Life Score; MDA: $\times 10^6$ dalton; MHz: Megahertz; SEM: Standard error of the mean; UPR™: Ultra-Pulsed Radioporation™

Introduction

Beginning with the baby boomer generation, the sight of a highly educated woman waiting for her first baby in her early to mid-thirties is ever more frequent in Western countries. Will she experience the humiliating symptoms of the involuntary loss of solid or liquid stool in the future?

The question may seem whimsical; she now looks so radiantly happy, but it is not: obstetric trauma has always been the leading cause of anal sphincter disruption, although often much deferred in time. Obstetric injuries may directly cause pudendal neuropathy but are usually unlikely to evolve into faecal incontinence (FI) before the woman is in her fifties: an observation that has long pointed to FI determinants as multifactorial [1]. Unsurprisingly, although 27.6% of women with index delivery complicated by anal sphincter disruption and 25.8% of women with episiotomy experienced troublesome FI,

so did 15.2% of women who had a caesarean section, according to a landmark 30-year retrospective study [2].

Coming back to our imminent mother in her thirties, forecasting her FI future in twenty years is hard. Obstetric advances and the steady decrease of mean parity per woman will continue to scale back two leading risk factors—direct damage to the sphincter complex and pudendal nerves. However, her likely long life will increase the risks of many conditions impacting the pelvic muscle tone and sphincter function—diabetic neuropathy, demyelinating and inflammatory bowel diseases, and rectal or perianal surgery or radiotherapy. Prolonged survival will also increase her lifelong burden of unfavourably acting drugs like antidepressants, anticholinergics, and laxatives [1].

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Advancing age is by itself a risk factor also because of the increasingly blunted rectal sensation and reflexes. The tendency for the sphincter and pudendal nerve efficiency is to worsen with ageing. Even if they do not, at least some progressions to lazy stool evacuation is likely, leading sequentially to delayed rectal stool retention and faecal impaction, prolonged relaxation of the internal anal sphincter, and possibly escape of liquid stool in the anal canal around the impacted faecal material, seepage, and undergarment staining [3].

FI is primarily a female problem, with about 9% of adult women experiencing episodes at least monthly, with urge FI and soiling the most frequent FI phenotypes due to pudendal neuropathy and diminished conscious contraction of the external anal sphincter [4,5]. Passive FI is the least common phenotype, probably due to unconscious and inefficient contractions by the external sphincter [5]. A population-based study in adult American women even suggested an incidence of up to 18.8%; in all cases, less than 30% of women seek care [6]. FI does not spare adult men, if only because 74% of inflammatory bowel disease patients experience FI at least once in their life and because of the expanding diabetic epidemic [6].

Even with severe FI (Wexner score 15 to 20), few patients progress to surgery while diet and drugs remain the mainstay treatments [7]. Mini-invasive, temperature-controlled radiofrequency energy delivery to the sphincter complex with nickel needles has complemented FI management for several years [8-10]. With a limit: the short-term moderate efficacy of the mini-invasive needle procedure completely wanes over the long-term, with no significant changes after five years in functional incontinence scales and the Fecal Incontinence-related Quality of Life Score (FIQLS), as well as in anorectal manometry and endoanal ultrasound imaging [9,10]. The efficacy of the mini-invasive radiofrequency technique, as measured by the Cleveland Clinic Florida Fecal Incontinence score (CCF-FI) or the Vaizey score, is already crumbling down to 10% of treated patients after only one year of follow-up [8,11].

The new non-invasive anatomical tip of the EVA™ device, based on the Dynamic Quadripolar RadioFrequency™ (DQRF™) technology, could change such disappointing outcomes in synergy with the Ultra-Pulsed Radioporation™ (UPR™) technology to facilitate the in-depth penetration of active principles. The paper illustrates the outcomes of the first study that explored the real-life FI effectiveness of the novel non-invasive radiofrequency technology.

Methods

Real-life study design, exploratory rationale, and cohort women's incontinence profile

A simple, prospective open design based on a small office-based cohort of 25 consecutive unselected women with faecal incontinence problems, nulliparous to multiparous, was deemed adequate for the first exploratory investigation of the DQRF™-based device designed explicitly for FI. The exploratory study, because of its intended real-life dimension, targeted a female population that experience medium-severity FI and everyday life disruption—the largest share of the ambulatory patients attending FI institutions and private practices. Candidate women should not have been taking medications known to affect collagen metabolism and neocollagenesis, such as non-steroidal anti-inflammatory drugs and corticosteroids, for at least one month.

Due to the preliminary and exploratory nature of the study, the investigators did not try to distinguish between incontinence variants such as soiling (accidental passage of small amounts of faeces with

staining or soiling of underpants), urge FI (urge to rush to the toilet to prevent FI or unavoidable defecation within 5 min after the first urge sensation), and passive FI (accidental passage of large amounts of solid stool with no urge sensation).

All study materials were peer-reviewed for ethical problems, and all enrolled women gave full written informed consent. Table 1 analytically illustrates the cohort women's baseline FI severity based on Jorge-Wexner categories and overall score and subscores. As usual, calculating individual scores meant cross-tabulating frequencies versus anal incontinence symptoms and consequences for daily life and summing up all individual subscores (score range extremes: zero for perfect continence and twenty for complete incontinence) [12,13].

The DQRF™ device

The non-invasive DQRF™ device derives from the DQRF™-based EVA™ device (Novavision Group S.p.A., Misinto, Monza-Brianza, Italy) and its advanced technology of algorithmically controlled radiofrequency energy delivery to gynaecological tissues [14,15]. The DQRF™ device incorporates a novel flat anatomical probe, ergonomically designed to adapt without trouble to the endorectal environment (Figure 1).

The four stainless steel electrodes on the elongated anatomical probe are the core of the proprietary 1.0-1.3 MHz DQRF™ technology. The DQRF™ device's maximum emitting power is 55 watts. The electrodes continuously cycle, under algorithmic control, between radio wave receiver and transmitter status, thus eliminating the grounding pad indispensable with standard radiofrequency technologies. In the ideal configuration and with the help of self-guided automatisms, the

Table 1. Baseline FI severity based on the Continence Grading Scale as described by Jorge and Wexner [12]. 0 ("never"); 1 ("less than one per month"); 2 ("less than one per week but more than once per month"); 3 ("less than one per day but more than once per week"); 4 ("more than once per day"). "Wears pad" category: needing disposable and reusable incontinence body-worn products (diaper-type garments or pads) with superabsorbent materials or disposable and reusable under-pads or bed-pads — and mean Wexner category subscores ± standard error of the mean (SEM).

Jorge-Wexner categories	Baseline mean subscores ± SEM
Solid	1.4 ± 0.65
Liquid	2.3 ± 0.63
Gas	2.6 ± 0.64
Wears pad	0.9 ± 0.91
Lifestyle alteration	1.2 ± 0.60
Wexner overall scores	8.6 ± 2.65



Figure 1. The novel probe of the non-invasive DQRF™ IF device, equipped with the dynamic quadripolar electrode system, is specifically designed to concentrate the radiofrequency energy in the anorectal sphincter complex area with high topographic precision and without invasive needles penetrating the sphincter muscle fibres.

repelling electric fields, generated within the four DQRF™ electrodes, concentrate the radiofrequency energy and its thermal effect with high tridimensional and layer precision in the 2 to 4 cm of the muscular anal tube and within the 0.3-cm to 0.5-cm thick, slow-twitch, fatigue-resistant smooth muscle expansion of the internal anal sphincter and the 0.6-cm to the 1.0-cm expansion of the levator ani muscles known as external anal sphincter.

By strongly reducing Ohm’s resistances in tissues, the DQRF™ technology maximises the intended goal of the radiofrequency treatment, thermal induction of neocollagenesis, while minimising the energy delivered and virtually eliminating all burn risk. Electronic movement and temperature sensors (RSS™, Radiofrequency Safety System technology) control the temperature in treated sphincter areas without systemic or local anaesthesia.

The FI DQRF™ device also exploits the previously described proprietary Ultra-Pulsed Radioporation™ (UPR™) technology to deliver a lenitive and pro-trophic mixture of two-third glucogel and one-third hyaluronic acid (molecular weight, 1.5 to 2.2 MDa, concentration 0.2%), previously spread on the tip, to the target sphincter complex areas [16]. UPR™ acts by opening aqueous channels in cell membranes through modulation of the DQRF™ radiofrequency effects. Genetic engineering has long exploited radiofrequency electroporation techniques to

maximise gene transfection efficiency and macromolecule penetration into cells [17,18].

The DQRF™ and pelvic floor exercise program

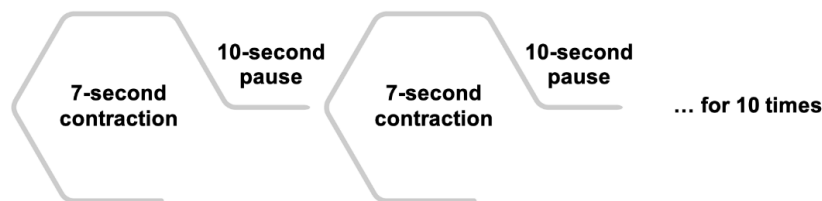
Preclinical investigations with the DQRF™ device in animal FI models and clinical experiences with other DQRF™-based devices in the female pelvic areas were crucial for designing the ideal radiofrequency IF treatment programs. The individually planned FI treatment cycles varied between five and eight weekly DQRF™ sessions performed according to the ethical standards laid down in the Declaration of Helsinki as revised in Brazil 2013.

Before each session, the device power was set at 20-25% of its maximum (no more than 13.75 watts) to reach tissue temperatures of 39-41°C in the target sphincter complex areas. Each “passive” DQRF™ session lasted 10 minutes, with the probe steadily inserted in the rectum.

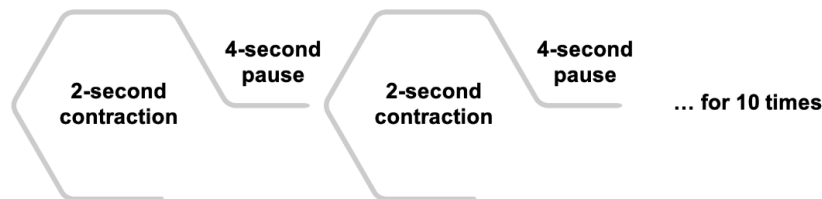
An “active” office program of tone-enhancing pelvic floor exercises without abdominal contraction followed each weekly “passive” DQRF™ session to train the smooth and somatic sphincter fibres (Figure 2). The women also performed thirty slow to rapid active muscle contractions at home twice daily during the non-invasive radiofrequency treatment program and were asked to repeat the program at least once every year.

Long-term pelvic tone maintenance program

1. Ten “resistance” muscle contractions — steady contraction (6-7 seconds) and 10-second muscle release (pause); each contraction/release cycle repeated for 10 times.



2. Ten maximum-strength and rapid contractions — rapid 2-second contraction and 4-second muscle release (pause); each contraction/release cycle repeated for 10 times.



3. Ten contractions with gradually increasing strength, each followed by 10-second muscle release (pause).

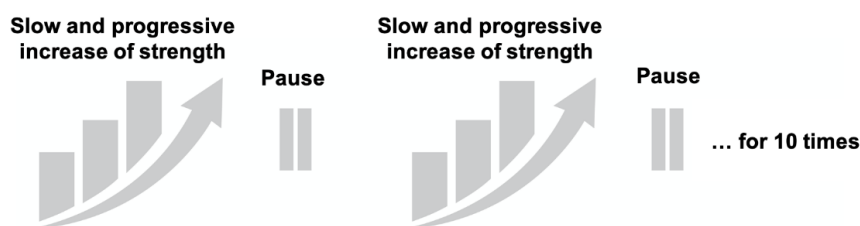


Figure 2. Pelvic floor exercises performed in the office after each DQRF™ treatment session and at home twice daily; program ideally repeated every year for long-term maintenance.

Wexner score assessments

Before the first DQRF™ + UPR™ session and after a pelvic exam, the investigators assessed the individual overall Jorge-Wexner scores and Wexner category subscores for each cohort woman; they repeated the complete assessment during the individual treatment cycle's last session. Follow-up control visit after about one more month.

Results

The 25 women included in the cohort had a mean age of 58.5 ± 9.89 years (median, 60.0 years; range, 30 to 71), with three women nulliparous and a mean cohort parity of 1.6 ± 0.87 (median, 2.0). The delivery had been natural in 18 women and caesarean in seven; all post-menopausal women had first experienced gas and stool incontinence only after menopause. Two women had systemic sclerosis; six had undergone haemorrhoidectomy and rectal surgery for cancer. Twelve women out of 25 underwent the shortest five-session DQRF™ + UPR™ program; seven women required six sessions, five women required seven sessions, and only one woman needed to undergo eight treatments. The overall mean number of non-invasive DQRF™ + UPR™ sessions was 5.8 ± 0.91 .

At the end of the individualised radiofrequency treatment cycles, the overall Wexner scores (final mean, 0.4 ± 0.58 , $p < 0.01$) had fallen to zero in fifteen cohort women and all women no longer needed incontinence body-worn products. One, five and four women still lamented occasional losses of, respectively, solid, and liquid stool and gas, and only one woman still referred some occasional impact on everyday life due to some occasional loss of gas. Even those residual liquid and gas incontinence appeared under control at the follow-up visit after one more month. Figure 3 illustrates the overall reported outcomes at the end of the DQRF™ + UPR™ cycle.

Discussion and conclusion

Within the anal sphincter complex, experimental physiology points to the 0.6- to 1.0-cm thick expansion of the levator ani

muscle known as external anal sphincter as the crucial target for all non-surgical options that complement the dietary, drug, and pelvic training mainstay FI management. The pressures developed within the anal canal are consistently higher than the pressures simultaneously measured endorectally during defecation [19]. Concomitant rectal radiographic imaging and anal electromyogram recording confirm the external sphincter and the puborectalis muscle as the main continence actors. The flap valve mechanism, exerting pressure on the anterior rectal wall and the puborectalis muscle and suggested in the seventies to have a leading role, appears less critical [19,20].

The new DQRF™-based technique correctly targets the crucial dysfunctional anal external sphincter. As documented in other districts prone to muscle laxities like the perineum and the vaginal vestibule, in the radiofrequency range 200 kHz to 3.3 MHz, the impedance-controlled energy delivered to tissue water molecules increases their Brownian random motion and frictional energy dispersion as heat (Figure 4) [14]. The rapid, controlled temperature rise triggers the deposition of new collagen and elastin networks, with tissue remodelling and local biomechanics improvements [14].

The same cascade of biophysical events applies to the remodelling of the sphincter complex scaffolding [21]. When applied to the anal canal up to 2.5 cm from the dentate line, the final morphological changes evoke the typical sphincter structure [21]. Only chronic conditions like anal Crohn's disease and distal ulcerative colitis contraindicate the radiofrequency energy delivery to the sphincter complex; the same applies to previous local radiotherapy.

The study has several weak points: the not so high number of cohort women, the open, uncontrolled design, the short follow-up, and assessing relief from stool or gas incontinence only through questionnaires, subjective and liable to a placebo effect. The bias linked to the uncontrolled placebo effect might be most disruptive, as it is likely with any condition that severely impacts everyday life. Baseline FI clinical severity was also not dramatic. However, the study in no way claims to demonstrate efficacy once for all and to establish a new FI

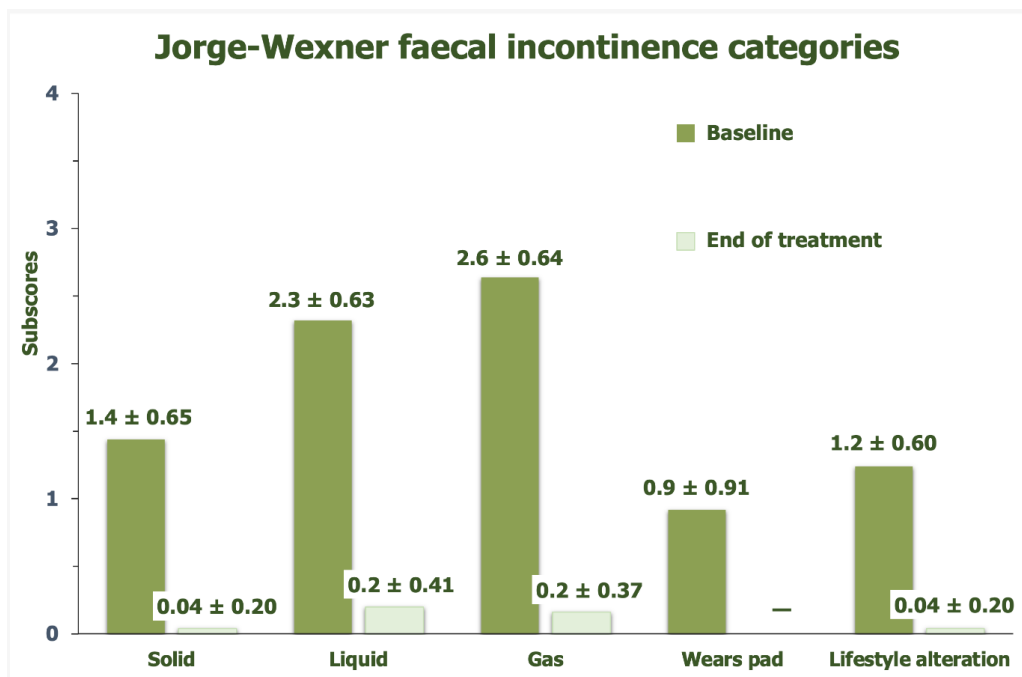
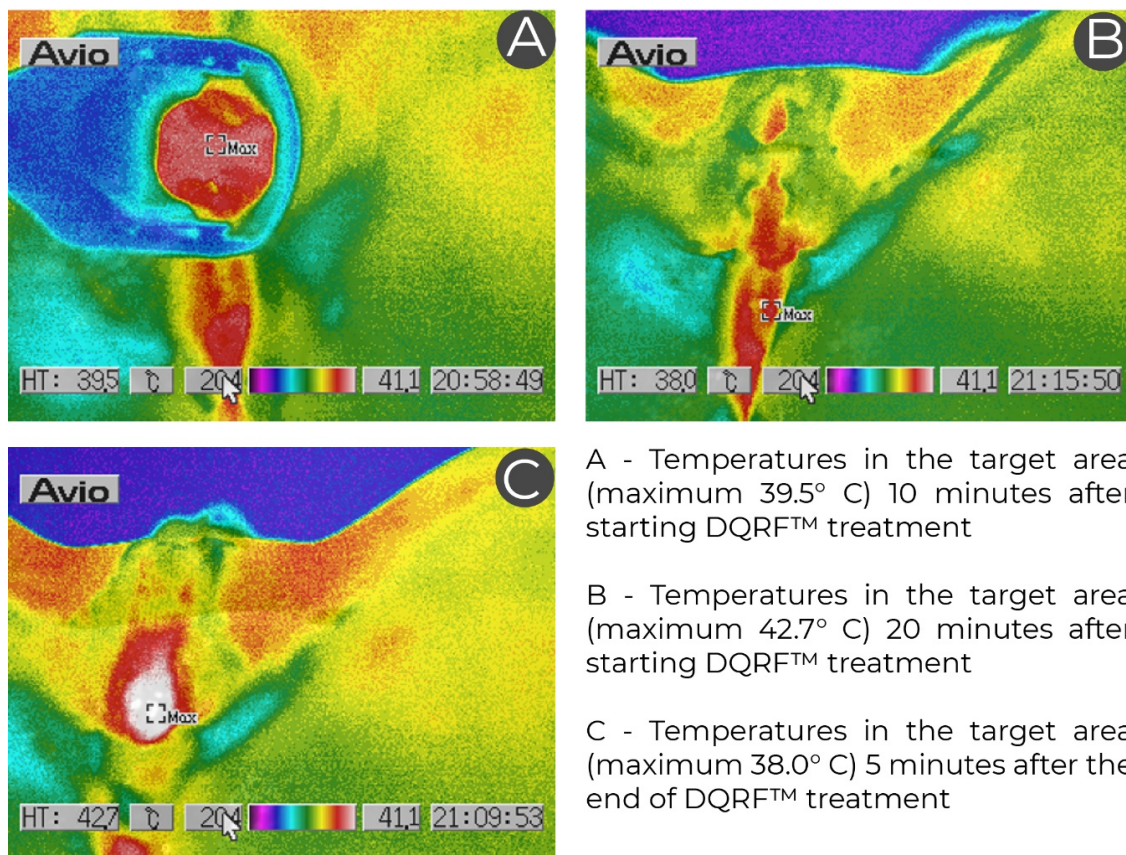


Figure 3. Jorge-Wexner FI category subscores at the end of the individual DQRF™ + UPR™ treatment cycles, mean ± SEM; $p < 0.01$ vs baseline for all five category subscores.



A - Temperatures in the target area (maximum 39.5° C) 10 minutes after starting DQRF™ treatment
 B - Temperatures in the target area (maximum 42.7° C) 20 minutes after starting DQRF™ treatment
 C - Temperatures in the target area (maximum 38.0° C) 5 minutes after the end of DQRF™ treatment

Figure 4. Sequential infrared photographs over 20 minutes in the perineal and vulvovaginal areas during a DQRF™ remodelling session (dorsal lithotomy position). Source: Novavision Group Spa Research & Development.

management standard. Exploring how sound is the rationale of non-invasively delivering radiofrequency energy to the sphincter complex was the sole aim—successfully reached, with 60% cohort women reporting complete FI control without untoward effects on the end of the DQRF™ + UPR™ sessions. The tendency for the residual, occasional (grade 1) loss of stool or gas in a few women at the end of the treatment cycle waned further at the follow-up visit after one more month.

Although needing caution because possibly prone to placebo effects and because coming from a small cohort, these exploratory outcomes will be most helpful to dimension the future trials that will give the definitive answer about how much effective is DQRF™ + UPR™ in faecal incontinence. Hopefully, future, well-designed studies will confirm the highly favourable subjective outcomes of this exploratory study over the long term. At least as significantly, well-designed studies will demonstrate that anal manometry and anorectal ultrasound improvements are steady over time. According to the most respected international scientific societies like the American Society of Colon and Rectal Surgeons and the American College of Gastroenterology, those crucial requirements are still unfulfilled by the currently available, minimally invasive radiofrequency technologies [22]. For the moment and waiting for more strong support, the DQRF™-based device lack of invasiveness looks like a definite benefit over existing radiofrequency technologies in FI management.

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