Diaphragm Pacing: Replacing, Delaying and Decreasing Mechanical Ventilators

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Conflict of Interest Disclosure

Raymond Onders M.D.
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University Hospitals of Cleveland

- Intellectual Property Rights
- Synapse Biomedical
  - Founder, Board Member

Objectives of the DPS Program

- Provide Natural Negative Pressure Ventilation with the patient's own diaphragm
- Provide it with limited trauma or risk
- Inexpensive
- Outpatient management
- Removable

Methods: Outpatient Laparoscopic Procedure

Simultaneous Gastrostomy Tubes

Methods: Visualizing the Diaphragm

Diseased/Denervated Muscle can be visualized

C3 SCI- Motor Neurons destroyed
Posterior diaphragm denervated

ALS- Radial bands of denervation

Laparoscopic Mapping of the Motor Point- Where Maximum Contraction Occurs

The key to finding the spot to implant electrodes

Onders, Aiyar, Mortimer. Am Surg 2004;70:241-7

Mapping the Diaphragm in ALS

Similar Patients Completely Different Surgical Observations

•Mostly UMN Involved Diaphragm
•FVC 60%

•Mostly LMN Involved Diaphragm
•FVC 50%
•Requires train stimulation to identify Motor Point

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Implanting Electrodes and Stimulating the Diaphragm

One electrode anterior diaphragm
One electrode posterior diaphragm

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Surgery can Predict Success in ALS Patients- No Ideal Preoperative Assessment

•Mostly UMN Involved Diaphragm
•FVC 60%

•Mostly LMN Involved Diaphragm
•FVC 50%

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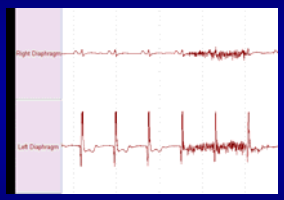
Methods: Continuous Diaphragm Burst monitoring- Biomarker Potential



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Intra-operative results: Positive to Negative Pressure Ventilation

Using DPS to Ventilate even after 28 years

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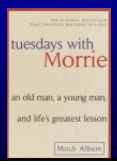
Electrode Characterization

- Setting optimized for each patient
  - Highest level with no discomfort
- Each diaphragm and electrode different settings
- Control options
  - Amplitude
  - Frequency
  - Rate
  - Pulse Width
  - Pulse Modulation

Delaying MV in ALS

- Upper and lower motor neuron disease
- Direct stimulation increases muscle mass
- Induction of nerve branching
- Afferent Trophic effects of stimulation
- Maintain Type 1(slow twitch) muscle fiber
- Overcome central sleep dysfunction



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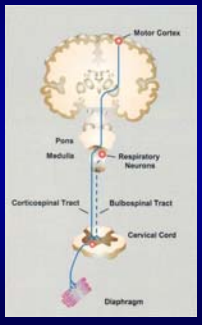
How Do We Breathe?
Consists of UMN & LMN Components



- UMN
  - Cerebral Cortex- volitional
  - Carotid Body
    - O2 saturation
  - Brainstem- Special somatic nuclei
    - CO2 levels
- LMN
  - C3-5
  - Small, medium and large neurons with different resistance levels
- Diaphragm Motor Units
  - Slow twitch Type I
  - Fast Twitch Type IIb

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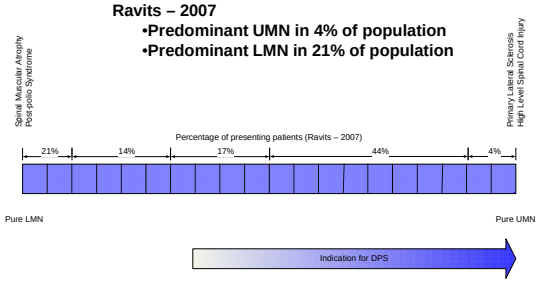
Indication for DPS Across UMN/LMN Distribution in ALS

Ravits – 2007
- **Predominant UMN in 4% of population**
- **Predominant LMN in 21% of population**



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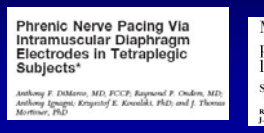
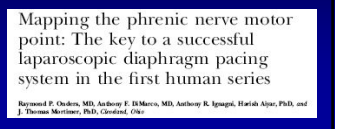
DPS Started for UMN Loss Spinal Cord Injury
Fifty Patient Pivotal
(Onders et al Surg End 2008)

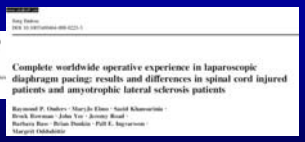
- 100% success in meeting tidal volumes for successfully implanted patients
- Over 50% use it 24 hours, 365 days a year
- Over 100 cumulative years of use- longest 8
- One year follow:
  - 100% had improved speech and more normal breathing
  - 100% increased sense of independence
  - 100% of patients prefer DPS
  - 100% recommend it to others

Publications Supporting UMN Use


Phrenic Nerve Pacing Via Intramuscular Diaphragm Electrodes in Tetraplegic Subjects*


Mapping the phrenic nerve motor point: The key to a successful laparoscopic diaphragm pacing system in the first human series


Diaphragm Pacing Stimulation System for Tetraplegia in Individuals Injured During Childhood or Adolescence


Complete worldwide operative experience in laparoscopic diaphragm pacing: results and differences in spinal cord injured patients and amyotrophic lateral sclerosis patients

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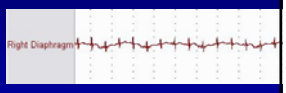
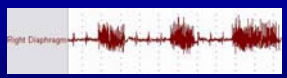
Implantation and Neuroplasticity

- Three patients have gone from Ventilators to DPS to volitional breathing
- DPS electrodes functions as EMG to assess recovery
- Can be used as a "biomarker" to assess other early aggressive therapies



Prior to DPS: NO EMG ACTIVITY



After DPS Conditioning: Recovery of Natural Function

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Conclusions 1: DPS to Replaces MV in Tetraplegics

- The DPS system is safe and effective
  - No significant device related adverse events
- All patients were able to utilize DPS for ventilation
- No patients stopped pacing and all would recommend it

All patients with an intact phrenic nerves should be offered diaphragm pacing to allow natural diaphragm breathing

Prospective Studies of DPS in ALS

Initial FDA design began 2003
clinicaltrials.gov

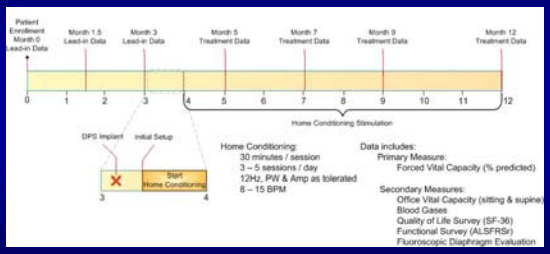
- **20 Patient Pilot Study**
  - 2004- 2007
  - 16 patients implanted / 4 patient fall-out
- **100 Patient Pivotal Study**
  - Approved October 2006, patients implanted 2007-8
  - 72 patients implanted / 28 patient fall-out
- *20 Patient French Study*
  - *1st patient implant Sept 2008*
  - *Will not be discussing results*

**Devices do not have phases of trial – Pilot to Pivotal

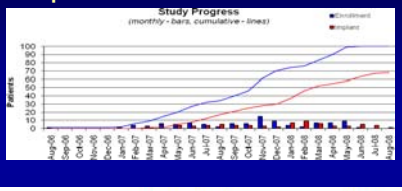
ALS Inclusion Criteria

- Bilateral phrenic nerve function as demonstrated by bilateral diaphragm movement with fluoroscopic sniff test or with EMG recordings and nerve conduction times
  - ***Excludes Predominant Lower Motor Neuron Disease***
- FVC between 50-85%
- FVC > 45% at time of surgery
- No general anesthesia contra-indications from medical co-morbidities

Methods Study Progression



Results: Enrollment and Implantation Pivotal Trial



	# (%) of Enrolled Participants	# (%) Implanted
UHCMC- Cleveland	41(41%)	32(44.4%)
Stanford- Palo Alto	14(14%)	7(9.7%)
Henry Ford- Detroit	10(10%)	7(9.7%)
CPMC- San Francisco	12(12%)	7(9.7%)
Mayo Clinic- Jacksonville	12(12%)	10(13.8%)
Methodist Hospital- Houston	10(10%)	8(11.1%)
Johns Hopkins- Baltimore	1(1%)	1(1.4%)
Total	100	72

Results: Reasons for Drop Out from Enrollment to Surgery

Pivotal 28 patients– (Pilot 4 patients)

- Did not meet inclusion criteria of FVC- 15(3)
  - F VC too high-2
  - FVC too low-13(3)
- Patients withdrew consent-12(1)
  - Patient Choice
  - Inability to cover surgical costs (insurance)
  - Unable to confirm diagnosis
- Investigator withdrew patient-1

Patient Demographics

19 (22%) were below 50% FVC
31 (35%) were hypercarbic

www.zeallsoft.com

mean ± SD [median] (N) or % (N)	G040142	
	Pilot(16)	Pivotal(72)
Age (years)	50.2 ± 9.6 [50.0]	56.0 ± 10.2 [56.5]
Gender (% Male)	81%	69%
Onset (% Bulbar)	25.0%	28.6%
Onset to Dx (mo)	15.5 ± 19.1 [8.5]	19.1 ± 20.0 [12.0]
Dx to Rx (mo)	22.8 ± 12.6 [19.5]	23.1 ± 18.1 [16.0]
Rilutek Use (%)	68.8%	75.0%
PEG (% at Surgery)	31.3%	31.9%
FVC at Implant (%)	59.6 ± 12.7	61.4 ± 11.7
Lead-In NIV Use	37.5%	65.7%

Results: Peri-operative

Two peer reviewed papers report surgical safety of implanting in ALS

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Results: Perioperative Adverse Events

Onders et al Surgical Endoscopy 2008

	SCI Subjects (n=50)	ALS Subjects (n=72)
Morbidity		
Wound Infections	1	2
Diaphragm Injury	0	0
Diaphragm Laceration	0	0
Solid Organ Injury	0	0
Bleeding	0	0
Bowel Injury	0	0
Conversion to Open	0	0
PEG Dislodgement	0	1
Pneumothorax	0	0
Capnothorax	21 (42%)	11 (15.3%)
Device		
Device Erosion	0	0
Device Migration	0	0
Lead Impedance Out of Range	0	0

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Results: Pilot Study DPS Increases Muscle Mass:

DPS converts Type IIb (fast twitch) to Type 1(slow twitch) muscle fibers

Test Location	Pre-implant	Post-implant	P-value
L @ expiration	3.9 +/- 0.7	4.8 +/- 1.2	0.02
R @ expiration	3.8 +/- 0.9	4.7 +/-1.1	0.01

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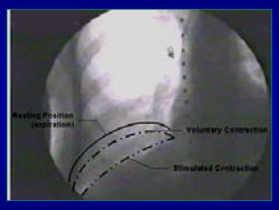
DPS Improved Movement of Diaphragm

Under Fluoroscopy

- **Increase in diaphragm contraction with stimulation compared to volitional movement**
- **Allows visualization of upper motor neuron involvement**



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Maintaining respiratory function in the face of progressing disease

ALSFR-r paired difference is statistically significant

Average is 9.6 +/- 11 (median 8%) [p value < .001]

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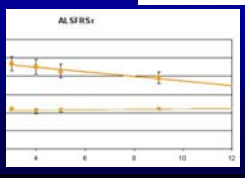
mean ± SD [median] (N) or % (N)	G040142	
	Pilot(16)	Pivotal(72)
ALSFRS-R at Implant	26.8 ± 7.0 [25.5]	28.0 ± 28.0 [27.3]
ALSFRS-R Ratio at Implant (% resp)	40.6 ± 11.7 [43.5]	32.7 ± 13.5[31.0]
ALSFRS-R Ratio Post Implant (%resp)	54.7+/- 17.9[56.5]	39.5+/-16.3[37.5]



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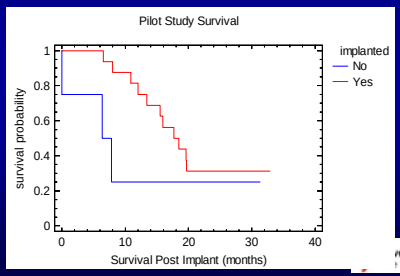
Results
Complete data on FVC decliners

- Rate of Decline Lead-In =
  - -2.7 ± 2.1 [-2.2](37)
- Rate of Decline Treatment =
  - -1.7 ± 1.6 [-1.6](37)
- Rate of Decline paired difference =
  1.1 ± 2.5 [1.1](37) p=0.01

Results Pilot: Survival

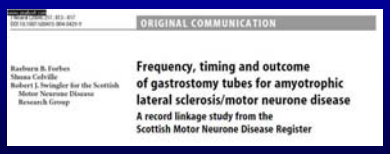
Red- implanted median survival from implant = 18 months
FVC (pre-implant) 60 ± 13 [45 - 89]
Blue- intent to treat (dropped out) median survival = 6 months
FVC (not implanted) 54 ± 10 [56: 40 - 64]



Results: Survival

19 Patients with FVC below 50%- Median Survival 16 months

Survival	DPS All	DPS w/ PEG	Forbes, 2004
30 day	103 / 103 (100%)	27 / 27 (100%)	75%
6 month	82 / 89 (92%)	24 / 26 (92%)	46%
12 month	64 / 77 (83%)	17 / 22 (77%)	23%

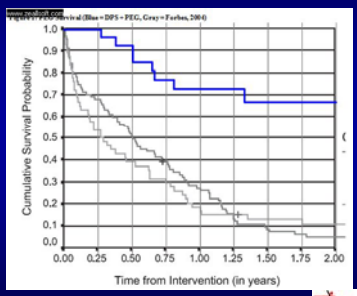

ORIGINAL COMMUNICATION

Frequency, timing and outcome of gastrostomy tubes for amyotrophic lateral sclerosis/motor neurone disease

A record linkage study from the Scottish Motor Neurone Disease Register

Gastrostomy and DPS Survival

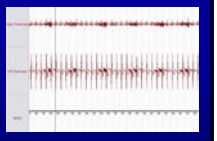
Compared to Forbes J of Neurology 2004



Analyzing the Deaths

Cause	
Respiratory	7(33%)
Withdraw DPS	6(24%)
Aspiration	3(14%)
Cardiac	2
Spinal Surgery	1
Fall	1
Accidental disconnect PPV still using DPS	1

Changing the mode of death
Patient losing communication
Still having spontaneous Diaphragm Bursts



Shortcomings of Study

- Patient Selection
  - Many traveled, perhaps higher socioeconomic status
- Air stacking to meet requirement of greater than 50% to enroll
- Survival affected by patients having to turn off device to die
- Because of worsening bulbar symptoms inability to get FVC late in the disease course
- Realization that FVC was not the appropriate measurement for efficacy of this trial

Critical "Other" Observations

- The most important findings were from our observations of the unexpected positive results we observed
- Listening to the patients allowed us insight into understandings respiration in ALS
  - LISTEN but then STUDY IT

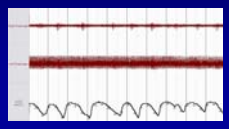
Key "other" results

#1. DPS treats central sleep apnea of ALS

"I'm sorry but I fell asleep with the device and it was my best sleep so I kept on using it at night"

- 24 of 48 patients use DPS during sleep (UHCMC)
- Split sleep study
  - Significant decrease of desaturations with addition of DPS

BIPAP ALONE- Repeated Desaturations

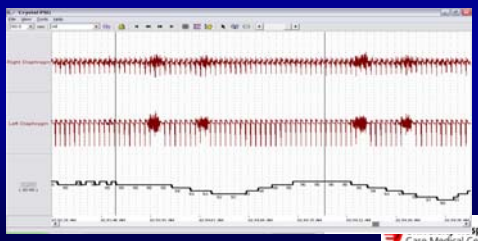


DPS and BIPAP- No Desaturations

#2 DPS Treats Respiratory Instability and Hypoventilation in ALS

"My husband may be developing that cognitive dysfunction"

Pt 01-11- DPS decreased pCO2 from 54 to 40
Patient became more alert



#3 DPS Increases Respiratory Compliance- "I DPS before I go out because I feel better"

Increased Respiratory Compliance decreases work of breathing

(Onders et al, Chest 2007)

- PPV causes posterior lobe collapse
- DPS ventilates posterior lobes
- DPS decreases atelectasis

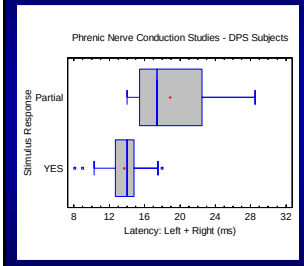
	PPV	PPV + DPS	% change
Respiratory Compliance	58 (ml/cm H2O)	69 (ml/cm H2O)	+19%

#4. FVC nor MIP adequately predicts diaphragm function

FVC 105% predicted- no R Diaphragm

Phrenic Nerve Studies and DPS

Prolonged Latencies predict worse response



- 41 Patients 16 ALS/25 SCI
- Good Responders N=30
  - Strong diaphragms
  - Latency 13.7 ± 2.2ms
- Partial Responders N=11
  - Weak diaphragms
  - Latency 18.9 ± 4.4ms

– Significant p<0.001

#5 DPS can overcome adverse diaphragm effects of NIPPV

"I was able to decrease my 20 hour a day use of NIPPV"

- All ALS patients should use NIPPV
- NIPPV- rests accessory muscles, helps overcome supine- sleep diaphragm dysfunction
- DPS- only maintains and stimulates diaphragm
- DPS and NIPPV can be utilized together

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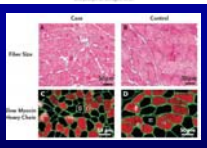
Positive Pressure Ventilation Damages the Diaphragm

- Compared 14 brain dead donors on PPV to 8 controls
- 18 hours of PPV causes marked atrophy
- 57% decrease Type 1 slow twitch
- Active muscles atrophy faster
- Inactivity leads to oxidative stress
- Increased proteolysis



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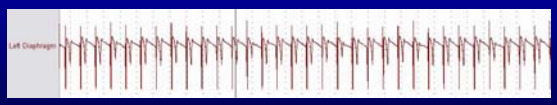
NIPPV Stops Diaphragm Activity

Sleep studies looking at diaphragm EMG shows no activity when on PPV- Making Diaphragm Weaker

Diaphragm EMG without PPV



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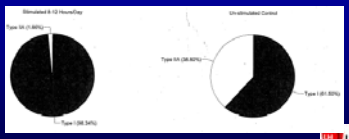
DPS Maintains Type 1 Muscle

Stimulated all Type 1

Un-stimulated- Type 1 and type 2



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ALS Implanted July 2007

Pacing helps him with the cheerleaders

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Conclusions

- DPS is safe and tolerated in ALS
- DPS positively affects diaphragm physiology
- DPS positively affects survival
  - Especially with PEG
- Augments NIPPV
- Provides "bio-marker" potential

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Can DPS decrease Mechanical Ventilation in the ICU?

- 1.6 million persons/yr (US) on mechanical ventilation
- 33-50% of ICU pts require mechanical ventilation
- 20% on ventilator > 7 days
- 40% time spent on weaning
- Over 100,000 tracheostomies performed yearly for failure to wean
- ICU costs $4000 per day
- Prolonged mechanical ventilation accounts for 37% of ICU costs(25 billion)

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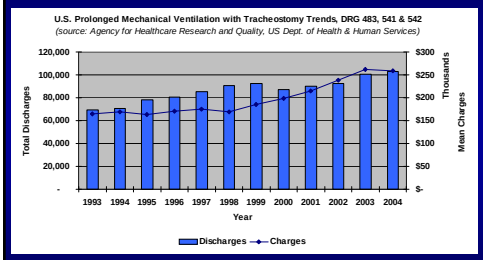
Mechanical Ventilation Increasing Use and Costs



Length of stay over past years is 40.2 +/- 0.6 days

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Problems of Mechanical Ventilation

Ventilator Induced Diaphragm Dysfunction (VIDD)

- Decreases Diaphragm Strength
  - Atrophy in 12 hours
  - Type I to Type IIb muscle conversion
- Increased Thoracic Pressure
  - Decreased cardiac output
  - Barotrauma
- Posterior Lobe Collape
  - Atelectasis and Pneumonia

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DPS with Ventilators

Onders et al Chest 2007

	MV	MV + DPS	% change
Respiratory Compliance	58 (ml/cm H2O)	69 (ml/cm H2O)	+19%
Peak Airway Pressure	22 (cm H2O)	14 (cm H2O)	-33%
Tidal Volume	834ml	961ml	+15%

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Diaphragm and Phrenic Nerve Dysfunction in the ICU

- Up to 25-30% of all cardiac cases with Ice or redo cases (Rousou, Efthimjou)
- Usually not cut- just demylinating injury
- Recovery 30 days to 2 years
  - 30% still present at one year
- Leads to atelectasis and recurrent pneumonias

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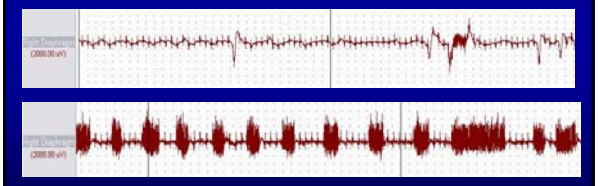
Patient with Transverse Meylitis:

First Reported Recovery of Phrenic and Diaphragm System From Use of DPS Confirms Feasibility of DPS use in Patients with Temporary Peri-operative Nerve Dysfunction (Up to 30% of cardiac cases Rousou, Efthimjou)



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Diaphragm Pacing in the ICU

- 100,000 tracheostomies for failure to wean
- PEGS and Lap DPS
  - Routine in ALS
- Diaphragm Pacing
  - Reduction in atelectasis
  - Improves compliance
  - Converts muscle to Type I
  - Increase diaphragm strength
  - Reduce barotrauma
  - Improves cardiac output

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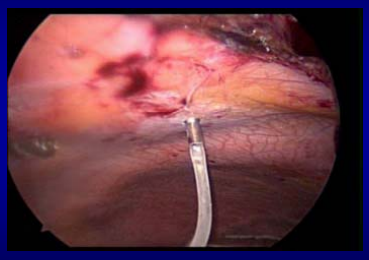
Next Generation: Binder Free DPS and Airway Clearance
Active Exhalation



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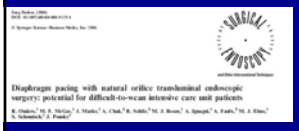
The Future-NOTES DPS



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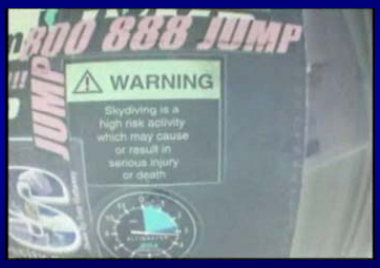
DPS increases the quality of life
You cannot skydive on a ventilator!



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Thanks

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