A follow up on more than 1000 children with cerebral palsy treated with HBOT What have we learned?

Dr.Pierre Marois, MD. FRCP(c)

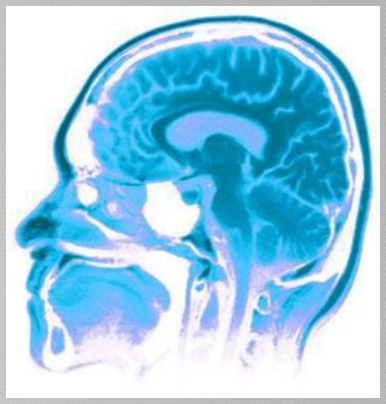
Ste-Justine University Hospital,

Montreal, Canada

- More than 60,000 consultations with children with cerebral palsy(CP)
- Regular follow-up of 1500 children with CP
- I am not involved with any clinics giving HBOT.
- I have initiated or participated in 4 studies on HBOT in CP

What is Cerebral palsy?

Cerebral Palsy



- *Définition : it is an umbrella term that describes a group of permanent neurological disorders caused by a brain defect or injury, that occured before or during birth or in the first few months of life.*

- *It is a non progressive condition characterized by motor and tone abnormalities.*

Causes

-Congenital (any brain injury or faulty development of the brain during intra uterine life)

-Anoxic-ischemic injury

-Vascular

-Trauma.

-Infection

Rationale for HBOT in CP

- Ischemic penumbra
- Neovascularizaton
- Increased metabolism and cell function
- Increased number of circulating stem cells

Gross Motor Function Measure (GMFM)

- Developed specifically for assessing changes in gross motor function
- Criterion-based observational measure
- 88 or 66 items

- **5 dimensions :**
  a) = lying and rolling
  b) = sitting
  c) = crawling and kneeling
  d) = standing
  e) = walking, running and jumping

0 = no initiation

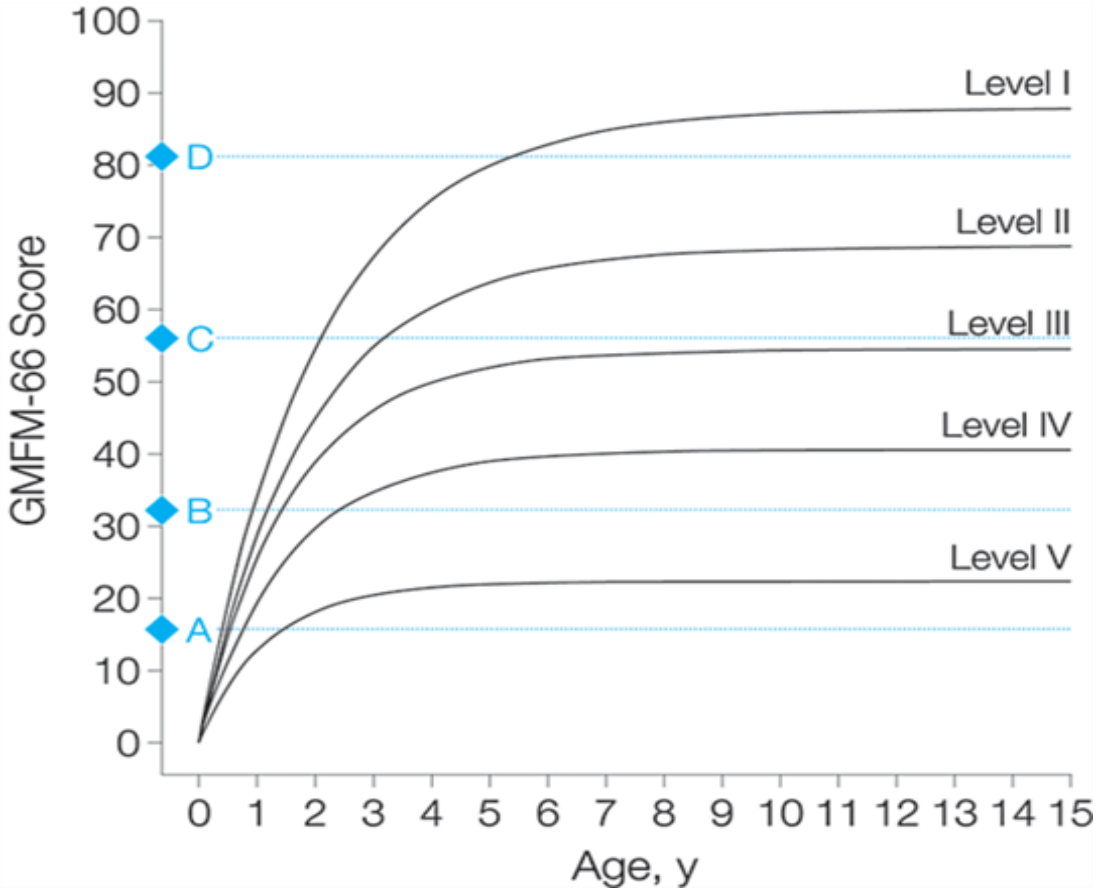
1 = initiated activity

2 = partially completed

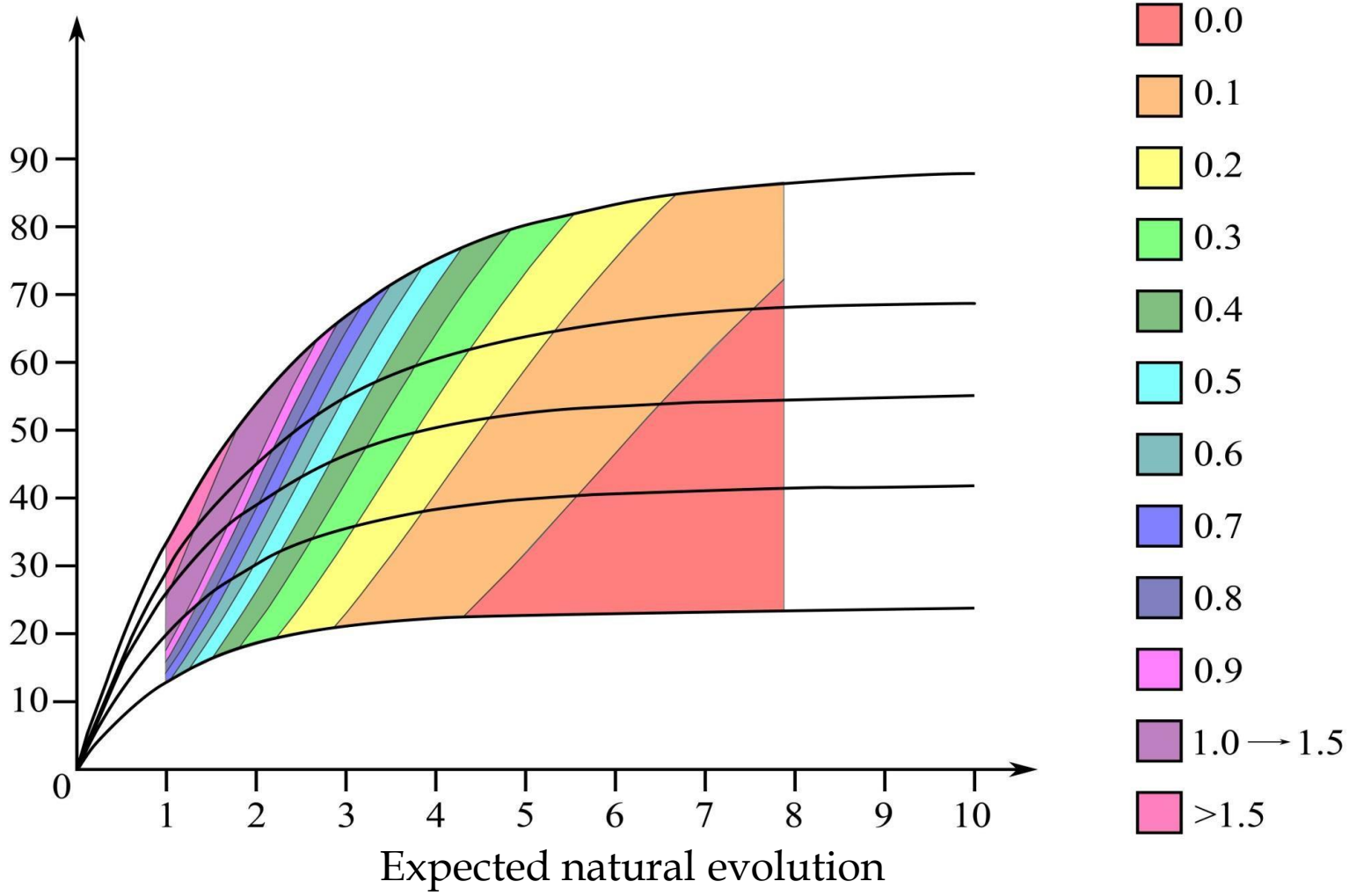
3 = completes activity

- Each item is scored on a 4-points scale :

GMFCS: Gross Motor Functional Classification Scale



Expected natural evolution in children with CP



How it all got started in 1998

Michel, Mathieu and Claudine

Support of Dr Richard Neubauer, Dr Paul Harch and Dr Philip James

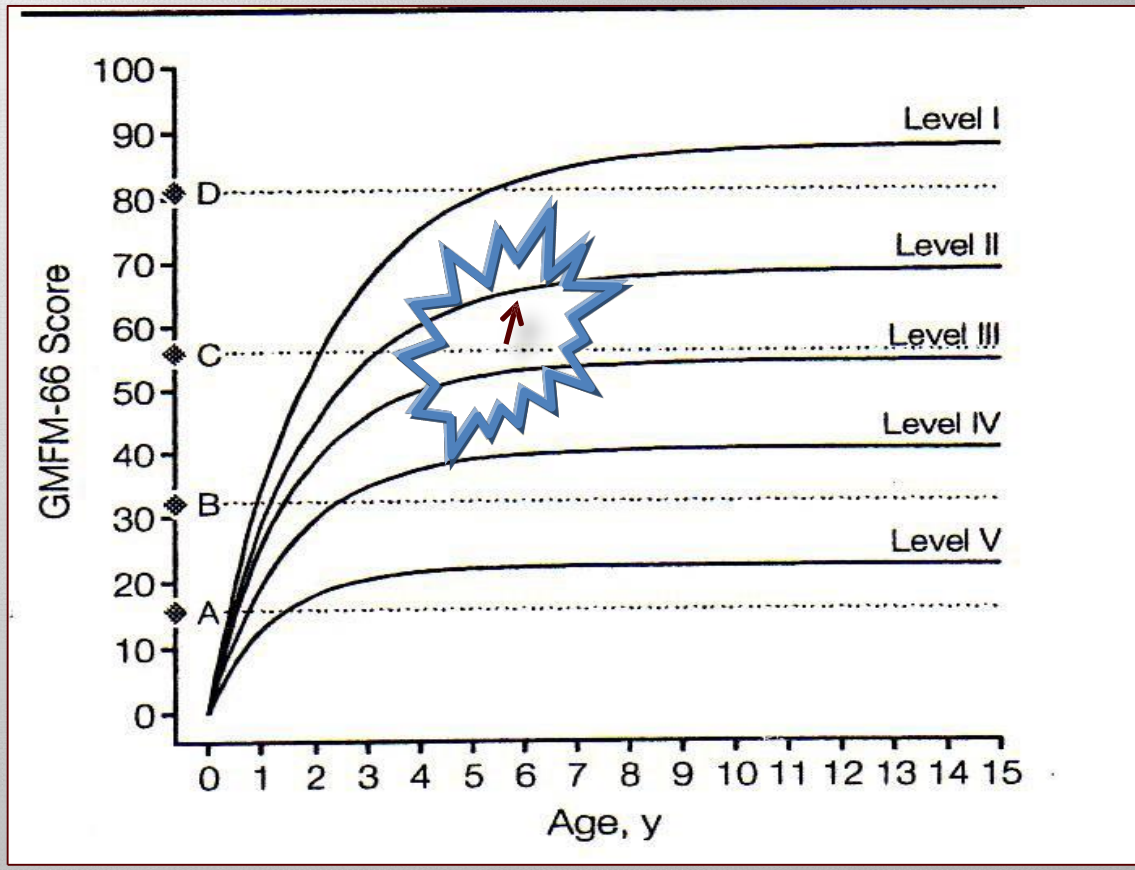
Pilot study (1998)

Pilot study (McGill 1998)

Montgomery D, Marois P, Goldberg J, Amar M, et al. Effects of hyperbaric oxygen therapy on children with spastic diplegic cerebral palsy: a pilot project. Undersea Hyperb Med 1999;26:235-242.

- 25 children with spastic diplegia
- 20 Tx, 1.75 ata
- Improvements in gross & fine motor skills
- GMFM improved 4.9% in one month

- Increased GMFM rate was 39 times greater than what was expected with natural evolution



Double blind study: The controversial Lancet article

Collet JP, Vanasse M, Marois P, et al. Hyperbaric oxygen for children with cerebral palsy: a randomised multicentre trial. Lancet 2001; 357:582-586.

- Published in « The Lancet » 2001
- 111 patients, 40 Tx, divided in two groups, no other interventions
- One group (HBO) treated at 1.75 ATA, 100% O2
- One group (HBA) treated at 1.3 ATA, 21% O2 (mild hyperbaric treatment or hyperbaric air)
- Genuine Control group removed by Collet

The data observed at end of study: Equivalent

BOTH GROUPS

Clinically and statistically improved with regards to:

- Gross motor function
- Memory, attention
- Functional skills

The Results

- The positive effects measured in both groups were similar and of the same magnitude (i.e. **not** statistically different)

- The 2 treated experimental groups improved respectively 36 & 25 times faster than what was expected with natural evolution!

However: Collet and Government position:

- This study demonstrated that HBOT in C.P. is ineffective…
- The impressive changes were secondary to a placebo effect… (even though there was no placebo or control group)

Just try to imagine a brain damaged child maintaining a placebo effect even three months after the HB Therapy was over !!!!

Lancet's Editorial
Quebec double blind study involving 111 children

- Although the results did not indicate that hyperbaric oxygen had any benifit over slightly pressurised air (mild hyperbaric treatment), they showed that both groups of children improved substancially with respect to gross motor function, speech, attention, memory and functional skills.
  The researchers postulate that either the two treatments were equally effective or the mere act of participating in a trial that promoted communication with other motivated children and parents had a positive effect.

Agency for H Agency for Healthcare Research and Quality (AHRQ). Systems to rate the strength of scientific evidence. Evidence Report/Technology Assessment no.47. Rockville, Md.: AHRQ; 2003. Available at: http://www.ahrq.gov/clinic/epcsums/hypoxsum.htm.Accessed Oct 21, 2007.healthcare Research and Quality (U.S.dept. of Health)

- The authors of the trial thought that the children in both groups improved because participation in the study provided an opportunity for more stimulating interaction with their parents. This is speculative, however, because there was no evidence to suggest that the parents and their children had less time together, or less stimulating interaction, before the study began…..
- **The possibility that pressurized room air had a beneficial effect on motor function should be considered the leading explanation.**

Editorial UHM 2012

- …this leads to confounding results and inappropriate abandonment of HBO_2T as a potentially valid therapy.
- The best example of this is the study of HBO_2T in cerebral palsy by Collet et al. in 2001 that, for many, is incontrovertible evidence that HBO_2T is ineffective for this condition [4]…
- We find it disconcerting that such a flawed study is forever after held up as the “gold standard” in the proof of HBO_2T’s lack of efficacy in cerebral palsy, despite other studies to the contrary [5].

Montreal Longitudinal study

Dr. P Marois
Dr. M Vanasse
Dr. Jean Lambert

- 200 files of patients treated (2001-2006)

- 120 cases retained for the study
  - C.P. diagnosis
  - More than 30 Tx
  - GMFM pre and post treatment
  - Two files excluded (results too impressive)

Characteristics

Nb:			**118**
Age			**6 years, 4 months**
Sexe	**M**		**61**
	F		**57**
Diagnosis	**Quadriparesia**	**87**	**73,7 %**
	Diplegia	**21**	**17,8 %**
	Hémiplegia	**6**	**5,1 %**
	Others	**4**	**3,4 %**
GMFCS	**Level**		
	1	**5**	**4,2 %**
	II	**16**	**13,6 %**
	III	**23**	**19,5 %**
	IV	**40**	**33 %**
	V	**34**	**28,8 %**

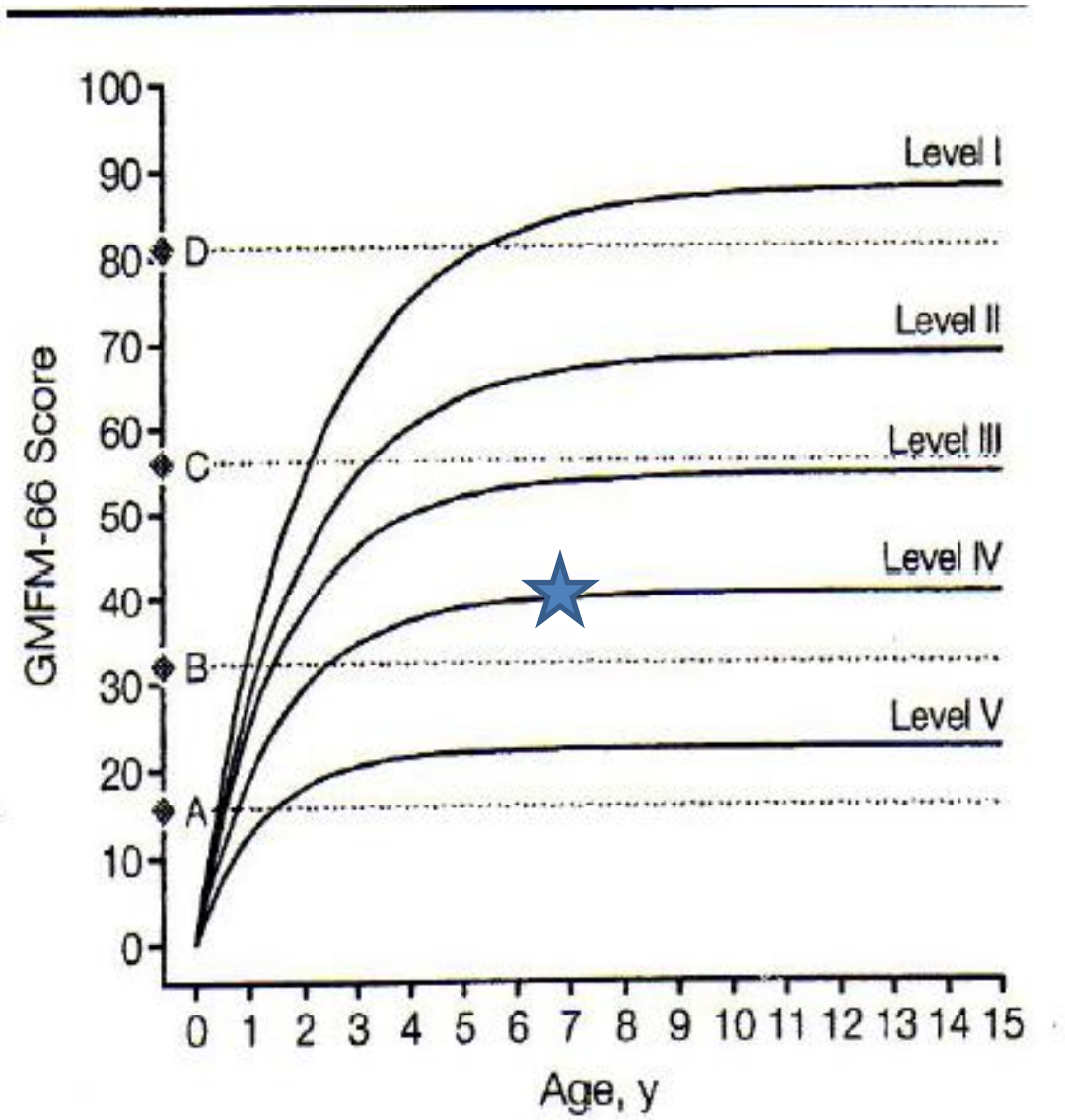
Treatment protocol

- **Protocol**
  - 1 hour, 5 days/week, 8 weeks of 1.5 ATA, 100% O2

- **Groups**:
  - One set of Tx: 118
  - Two sets of Tx: 40
  - Three sets of Tx: 20

- **Evaluations**
  - GMFM
    -Pre treatment
    -2 months post treatment

Nb	118		
Age	76,36 months	(6 years, 4 months)	± 6,9 months
Nb Tx	39,0		± 0,6
Evaluation interval	3,9 months		± 0,16
GMFM pre treatment	36,73		± 2,68


GMFM-66 Score
100
90
80
70
60
50
40
30
20
10
0
D
C
B
A
Level I
Level II
Level III
Level IV
Level V
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Age, y

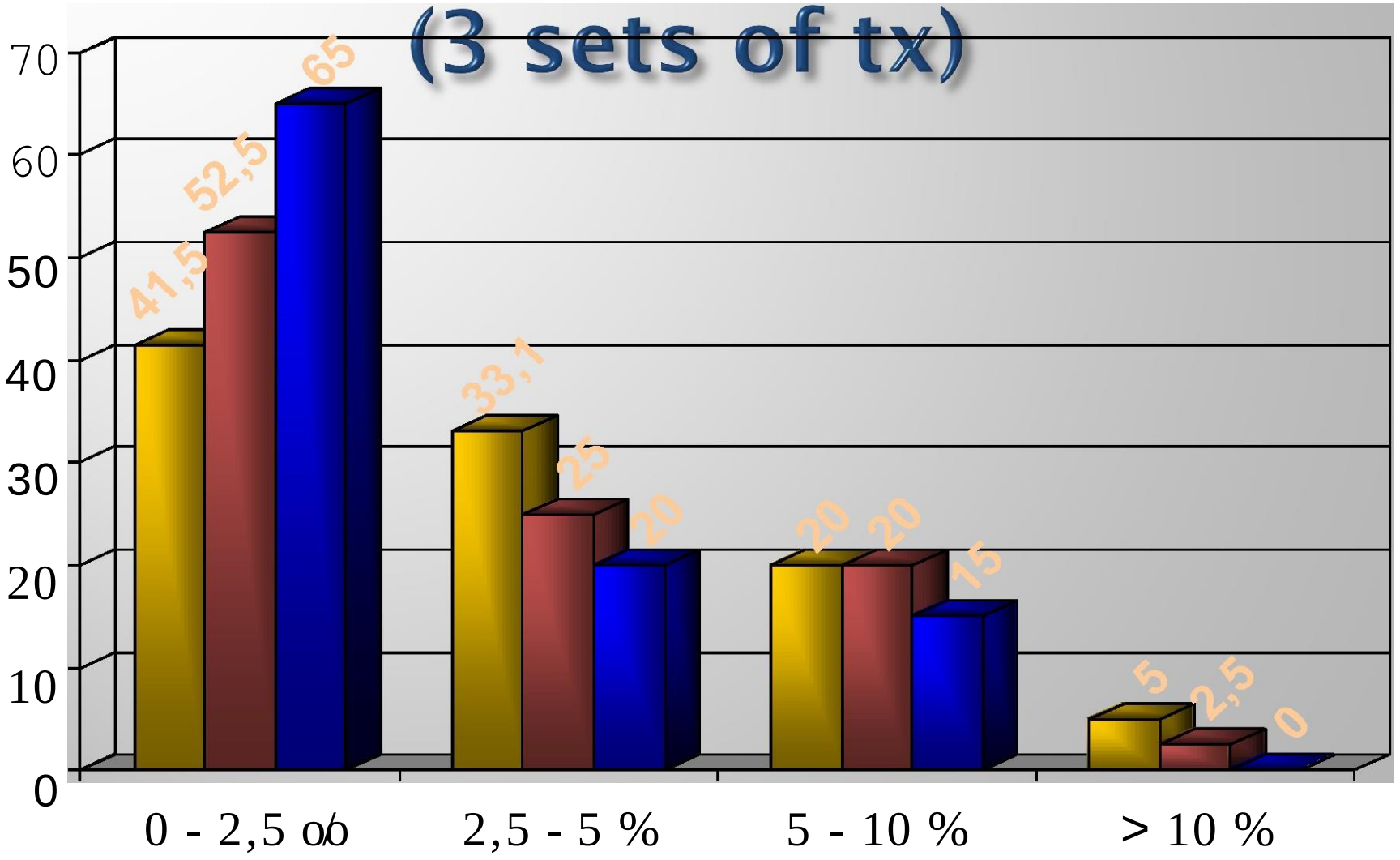
Data

	GMFM change	P. Value
Pre GMFM 1 n:118	3,96 %	0,000
Post GMFM 1		
Pre GMFM 2 n:40	3,09 %	0,000
Post GMFM 2		
Pre GMFM 3 n:20	1,77 %	0,058
Post GMFM 3		

For all the patients

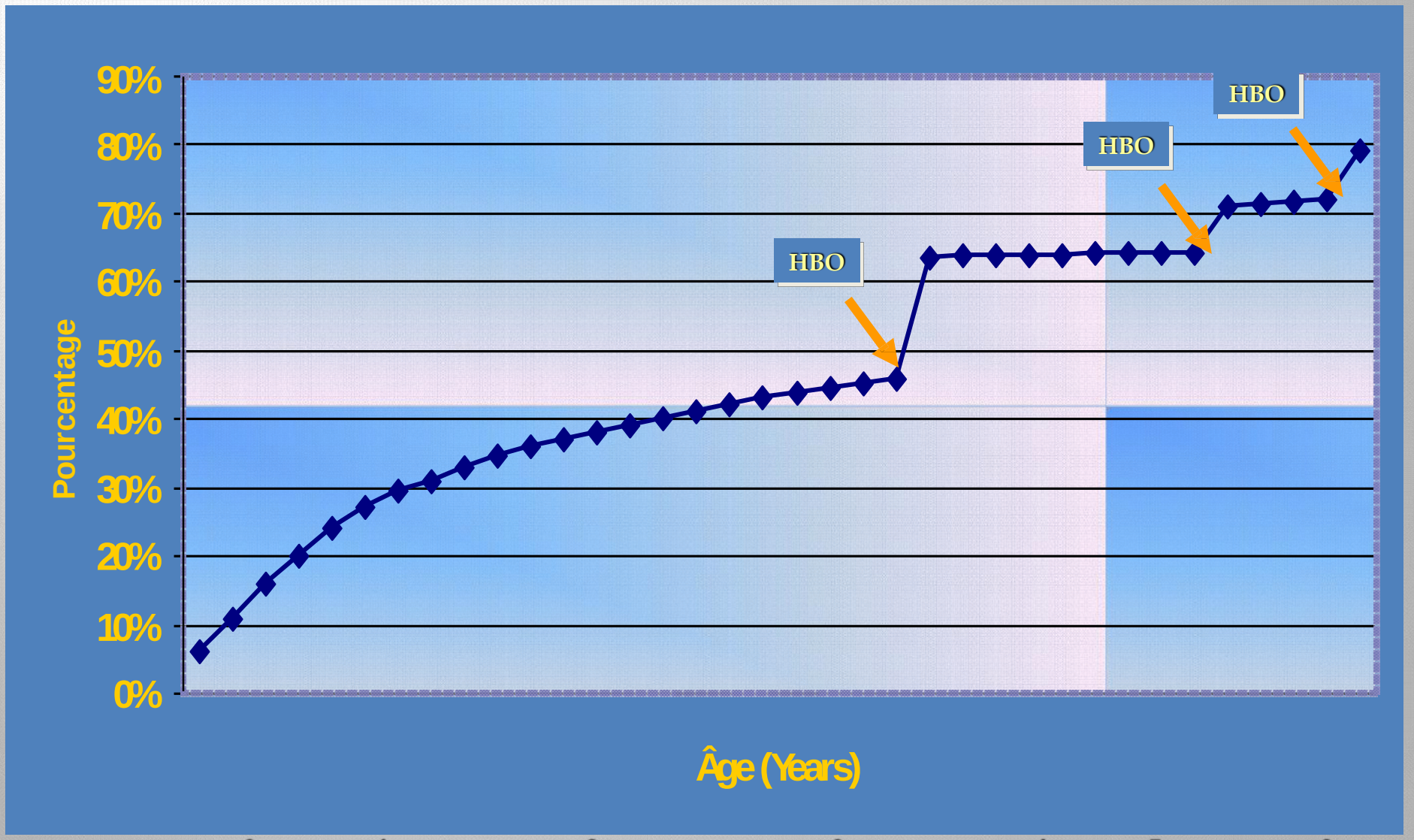
# Set of Tx	Nb of patients	Nb of Tx	Pre GMFM	GMFM Change	Relative change
Set # 1	118	39	36,7	3,9	19 %
Set # 2	40	33	34,6	3,0	16 %
Set # 3	20	35	30,4	1,8	8 %

% of children vs GMFM change



GMFM Results

K.B.



Other observations

> 80 % of parents reported:

- cognitive changes
- Fine motor changes
- Communication skills

CONCLUSION

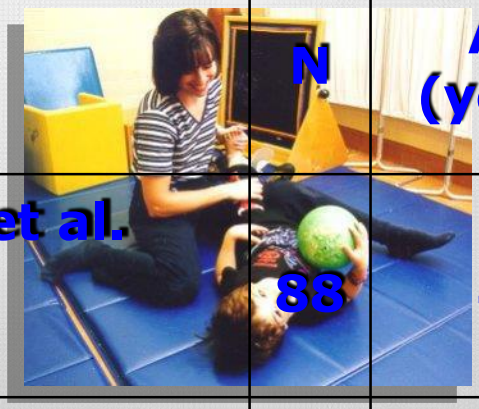
- In this study, analysing the effects of HBOT in C.P., we found that the vast majority of children improved significantly (statistically and clinically) their gross motor function.
- This confirms the impressive changes measured in our two previous studies.

Other studies (using GMFM as evaluation tool)

- Ref: Sénéchal C, Larivée S, Richard E, Marois P. Hyperbaric oxygenation therapy in the treatment of cerebral palsy: A review and comparison to currently accepted therapies.
- Journal of American Physicians and Surgeons. 2007; 12: 109.

Other studies (using GMFM as evaluation tool)

1. Physiotherapy



	N	Age (years)	Change	Time frame	Rate of change
Russel et al. (1989)	88	4,9	3,7	6 mo	,6/mo
Trahan et al. (1999)	50	3,7 ± 1,6	5,7	8 mo	,7/mo

Other studies (GMFM)

2. Selective Dorsal Rhizotomy ± Physiotherapy *					
	n	Age (years)	Change	Time Frame	Rate of change
Hays et al. (1998)	92	7,5 ± 3,98	5,2 ± 1,8	12 mo	,5/mo
Nordmark et al. (2000)	18	2,5 – 6	9,6	12 mo	,8/mo
Wright et al. (1998) *	24	4,8 ± 1,11	11,8	12 mo	1,0/mo
McLaughlin et al. (1994) *	34	7,6 ± 3,65	9,6 ± 6,9	12 mo	,8/mo
Steinbok et al. (1997) *	30	4,1	11,3	9 mo	1,2/mo
McLaughlin et al. (1998) *	43	6,45 ± 3,6	7,2	24 mo	,3/mo

Other studies (GMFM)

3. Orther interventions

	n	Age (years)	Change	Time Frame	Rate of change
Damiano et al. (1998) *Strength Training*	11	8,8 ± 2,3	1,1	6 wks	,8/mo
Steinbok et al. (1997) *Electrical Stimulation*	44	7,3	5,9	12 mo	,3/mo
Almeida et al. (1997) *Intrathecal Baclofen*	1	11	6,4	24 mo	,3/mo
Law et al. (1998) *Family Centered Functional Therapy*	5	Under 4	17,7 (Goal area only)	3 mo	
McGibbon et al. (1998) *Equine*	5	9,6	7,4 (E only)	8 wks	

Other studies (GMFM)

3. Other interventions (suite)					
HBO	**n**	**Age (years)**	**Change**	**Time Frame**	**Rate of change**
Montgomery et al. (1999) HBO	25	5,6 ± 1,6	4,9	1 mo	4,9/mo
Collet et al. (2001) HBO	111	7,2	3,0	2 mo	1,5/mo
Marois et al. (2006) HBO	118	6,4	3,9	3,9 mo	1,0/mo

Conclusion

In the three studies conducted in Quebec the amount & the rate of progress were more important than those observed with other recognised therapies in C.P.

Studies with HBOT in CP

Ref: Sénéchal C, Larivée S, Richard E, Marois P. Hyperbaric oxygenation therapy in the treatment of cerebral palsy: A review and comparison to currently accepted therapies.

Journal of American Physicians and Surgeons. 2007; 12: 109.

Machado (1989)

Sao Paulo, Brazil

- 230 patients
  20 TX
  Decrease in spasticity in 94% of the cases. 6 months post-treatments: improvement in cognitive functioning or in level of spasticity in 75.6% of the children.

Cordoba-Cabeza (1998)

Las Tunas, Cuba

- 14 patients
  20 TX
  A satisfactory response was observed among patients treated in the first year following the lesion, with more significant and more rapidly obtained results.

Montgomery, Marois et al. (1999)

Montreal, Canada

25 patients
20 Tx
The results show an increase in gross motor functions in 3 of the 5 items of the Gross Motor Function Measure (GMFM), an increase in fine motor functions, and a decrease in spasticity.

Barrett (1999)

University of Texas at Galveston, USA

- 14 patients
  60 TX
  Hyperbaric oxygen therapy produced increases in the assessment of gross and fine motor functions, and decreased spasticity among patients with cerebral palsy.

Packard (2000) .

Cornell University, USA

- 26 patients
  40 TX
  Among some children with moderate to severe cerebral palsy, there is evidence that HBOT improves motor skills, attention, language, and play.
- While the treatment is not curative nor miraculous, the changes are often substantial

Waalkes et al. (2002)

U.S Army

- 8 patients
  80 Tx
  The assessments compared pre- and post-treatments using several functional measures. HBOT demonstrated an increase in gross motor functions and a decrease in total time of necessary care for children with cerebral palsy.

Sethi and Mukherjee (2003)

New-Delhi, India

- 30 patients
  (15: HBOT + occupational therapy
  15: occupational therapy alone)
  40 Tx
  Rate of progress in gross motor functions of the test group (HBOT + occupational therapy) is much more rapid than that of the control group (occupational therapy alone).

Marois and Vanasse, (2006)

Montreal, Canada

118 patients
40 Tx
Significant increases in the GMFM of 3.96% for the entire group of subjects.

The only negative conclusion …

Effects of Hyperbaric Oxygen on Motor Function in Children with Cerebral Palsy

ANN NEUROL 2012;72:695-703

Daniel J. Lacey, MD, PhD,[1,2] Adrienne Stolfi, MSPH,[2] and Louis E. Pilati, MD[3]

Variable		HBO, n = 25	HBA, n = 24	*p*
Age, mean ± SD, range		6.3 ± 1.3, 3.8-8.2	5.2 ± 2.0, 3.0-8.4	0.027
GMFM-88 score	(%, mean ± SD)	38.2 ± 32.3	42.0 ± 30.3	0.673
GMFM-66 score	(mean ± SD)	39.5 ± 19.6	40.7 ± 20.1	0.838

Lacey's study analysis

- Small number of children
- Control group was not a placebo but a different dosage of hyperbaric treatment. (14% O2, 1.5 ATA)
- A placebo treatment cannot be a treatment with unknown effects!!
- Unethical? (Breathing more nitrogen)
- **Self aborted study because unreachable objectives (5% GMFM increase…never obtained with any treatments for CP) could not be reached!**

What lead to the UDAAN Study?

- The only doubt subsisting was created by the removal of the control group in the double blind study…and the controversial interpretation of the results.

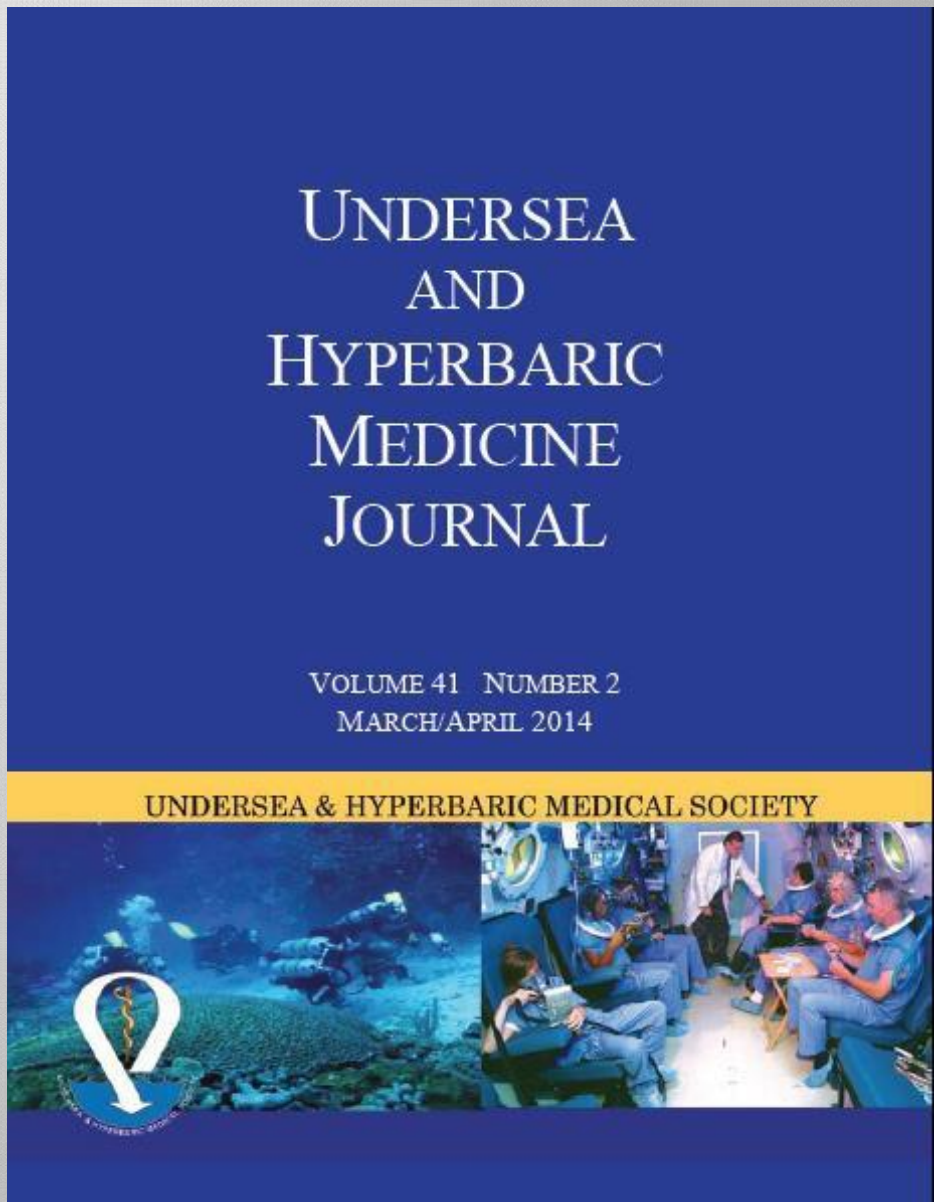
- To dissipate this doubt we had to conduct a research evaluating the effects of the two dosages of HBOT used in the double blind study in comparison with the evolution a control group.

UDAAN HBOT STUDY

Dr. Arun Mukherjee
MBBS, MD (Medicine)
Sr. Consultant in Internal Medicine
Fellow of Medical Academy of Pediatric Special Needs (USA)
Founder Trustee
UDAAN for the Disabled

The Journal

- The Gold Standard Journal for HBOT data and facts



Ifhe Paliticipants of the UDAAN HBOT Study

UHM 2014, VOL. 41 NO 2 - HB02 THERAPY IN CHILDREN Win i CEREBR:AL P LSX

Intensive rehabilitation combined with HB0 2 therapy in children with cerebral palsy: A controlled longitudinal study

A.run Mukherjee M D. 1; Maxime Raison Ph.D. 2; Tarun Sahni M.D. 3; Anand Arya MPt 4 Jean Lambert Ph.D.5 Pierre Marois M D. ; Philip B. James M.B. 6; Audrey Parent B.Sc. 2; Laurent Ballaz Ph.D 2

1 Shubham Ho.spital, Kalkaj New Delhi, India; 2Centre de Readaptation Marie-Enfant, Center Hospitalier Universitaire Sainte-Justine, Montreal, Quebec, Canada; J Indraprastha Apollo Hospital New Delhi, India; UDAAN for the Disabled Project of FSMHP C-27 Dayanand Colony, Lajpatnagar, New Delhi, India;, Department of Social and Preventive Medicine, School of Medicine, Univer de Montreal, Montreal Quebec Canada, 6 Professor Emeritus, University of Dundee, Nethergate, Dundee, Scotland

CORRESPONDING AUTHOR: Lauren Ballaz Ph.D *Laurent.ballaz@uqam.ca*

Aims and Objectives

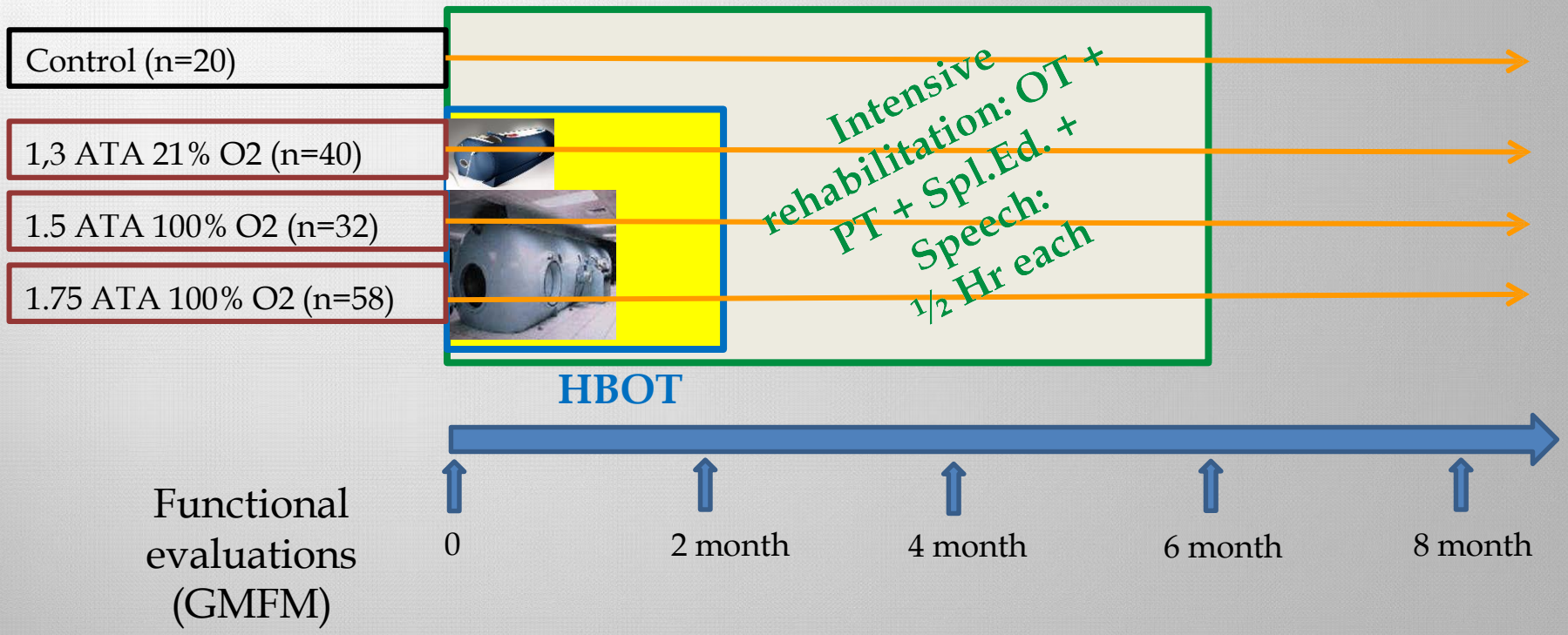
- Safety of various pressures
  - Study the long term safety of Hyperbaric Oxygen Therapy (HBOT) in children having Cerebral Palsy (CP) due to Hypoxic Ischemic Encephalopathy (HIE) before, during or within 2 years of birth.

- Comparative efficacy of various pressures:
  - Study the comparative benefits if any of various degrees of HBOT pressures and oxygen levels that could not be a part of the Lancet 2001 study.

Sequential Evolution of the four Groups

- **Control**:
  - Children who did not opt for Hyperbaric Therapy were included as the control group (n = 20).
- **2001**:
  - UDAAN started the then-prevalent 1.75 ATA 100% O_2 90 min HBOT x 40 sessions for children with CP along with Standard Rehab (n=58).
- **2004**:
  - Based on guides by Harch & Wassman (4th Int. Symp. on HBOT & the Brain Damaged Child, FL, 2004), we started 1.5 ATA 100% O_2 HBOT (n=32)
- **2006**:
  - To complete the series as per the Collet study (Lancet 2001), we started mHBOT using room air at 1.3 ATA in a soft chamber (n=40).

Method



Hyperbaric treatments:, 6d/week, 40 treatments,
1 Hr/day at pressure plus time to compress / decompress

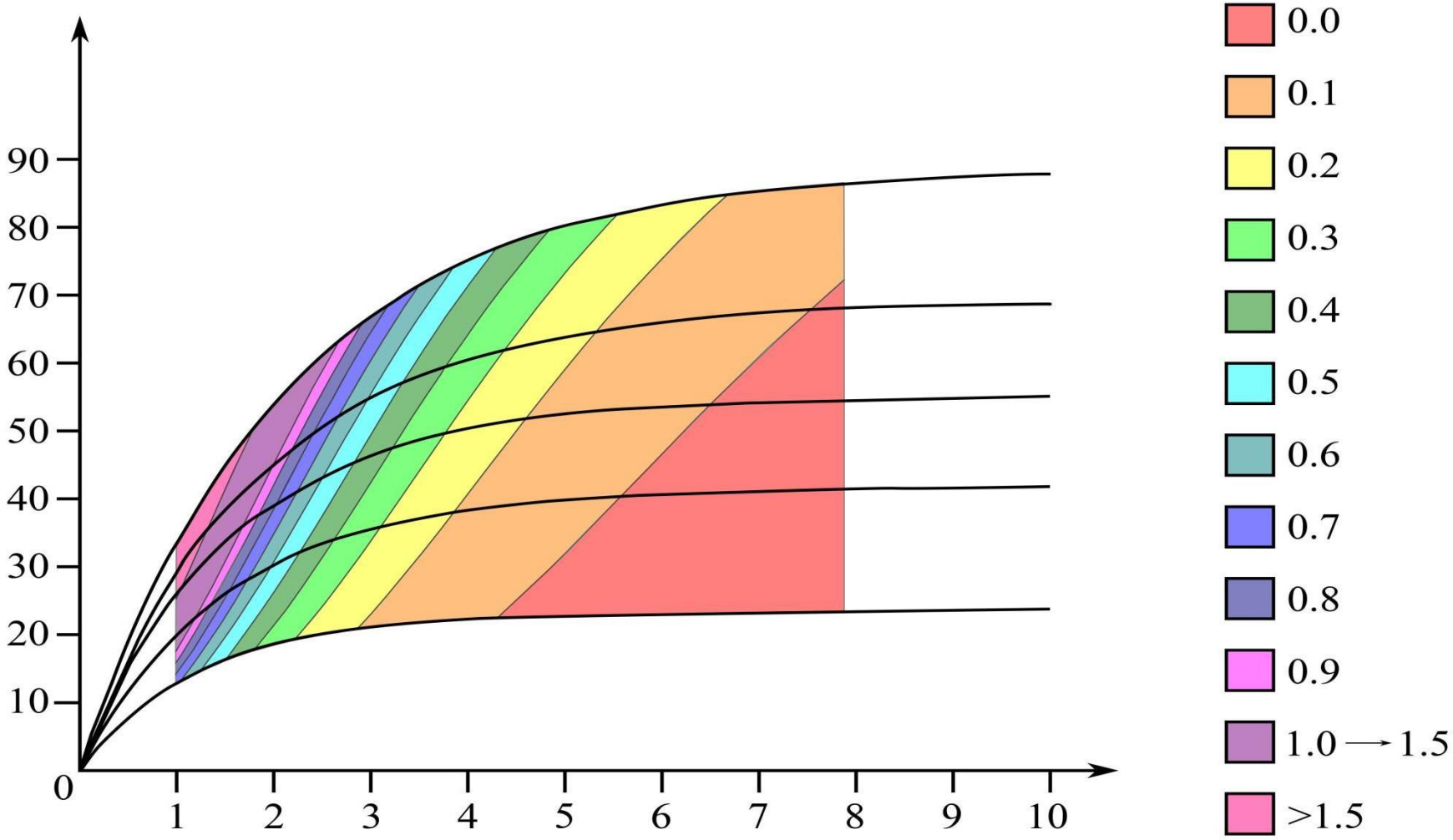
Intensive rehabilitation: 2h/day, 6d/week, during 6 months & contd.

Table 1: Participants Characteristics

Groups	Diagnostics	Gender (M/F)	Age (yrs) Mean (range)	GMFM baslinescore Mean (SD)
Control (n=20)	Athetoid CP, n=2 Hemiplegic CP, n=2 Diplegic CP, n=2 Quadriplegic CP, n=12	13/7	35 (1 to 17)	29.6 (13.0)
1.3 atm abs (11=40)	Athetoid CP, n=3 Hemiplegic CP, n=0 Diplegic CP, n=16 Quadriplegic CP, n=12	29/11	4.9 (1 to 11)	29.6 (14.8)
1.5 atm abs (11=32)	Athetoid CP, n=3 Hemiplegic CP, n=1 Diplegic CP, n=15 Quadriplegic CP, n=13	23/9	4.3 (1 to 12)	34.3 (15.6)
1.75 atm abs (n=58)	Athetoid CP, n=6 Hemiplegic CP, n=2 Diplegic CP, n19 Quadriplegic CP, n=31	40/18	4.3 (1 to 13)	32.5 (11.8)

atm abs = atmosphere absolute; CP = cerebral palsy; F = female; GMFM = gross motor function measurement, M = male.

GMFCS


90
80
70
60
50
40
30
20
10
0
1
2
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6
7
8
9
10
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0 → 1.5
>1.5

Evaluation Procedures: GMFM & GMFCS

The children were evaluated at 0, 4, 6 months and also at 2 and 8 months where possible by the same group of therapists that were accustomed to assessing the evaluations.

Each evaluation consisted of the following tests:

Gross Motor Function Measurement (GMFM; ref: Palisano,1997**)**: This scale gives a dual result of mean improvement at serial intervals based on a 66 point scale, and an enlarged parameter level of 88 points that assesses motor function in 5 dimensions:

A	LYING AND ROLLING,
B	SITTING,
C	CRAWLING AND KNEELING,
D	STANDING, AND
E	WALKING, RUNNING AND JUMPING.

- Each item is scored on a 4-points scale (0, 1, 2, 3) and the test gives numeric results for each dimensions (GMFM-88) as well as a total score (GMFM-66).

Gross Motor Functional Classification: This is a measure of degree of severity of disability on 5 levels**.**

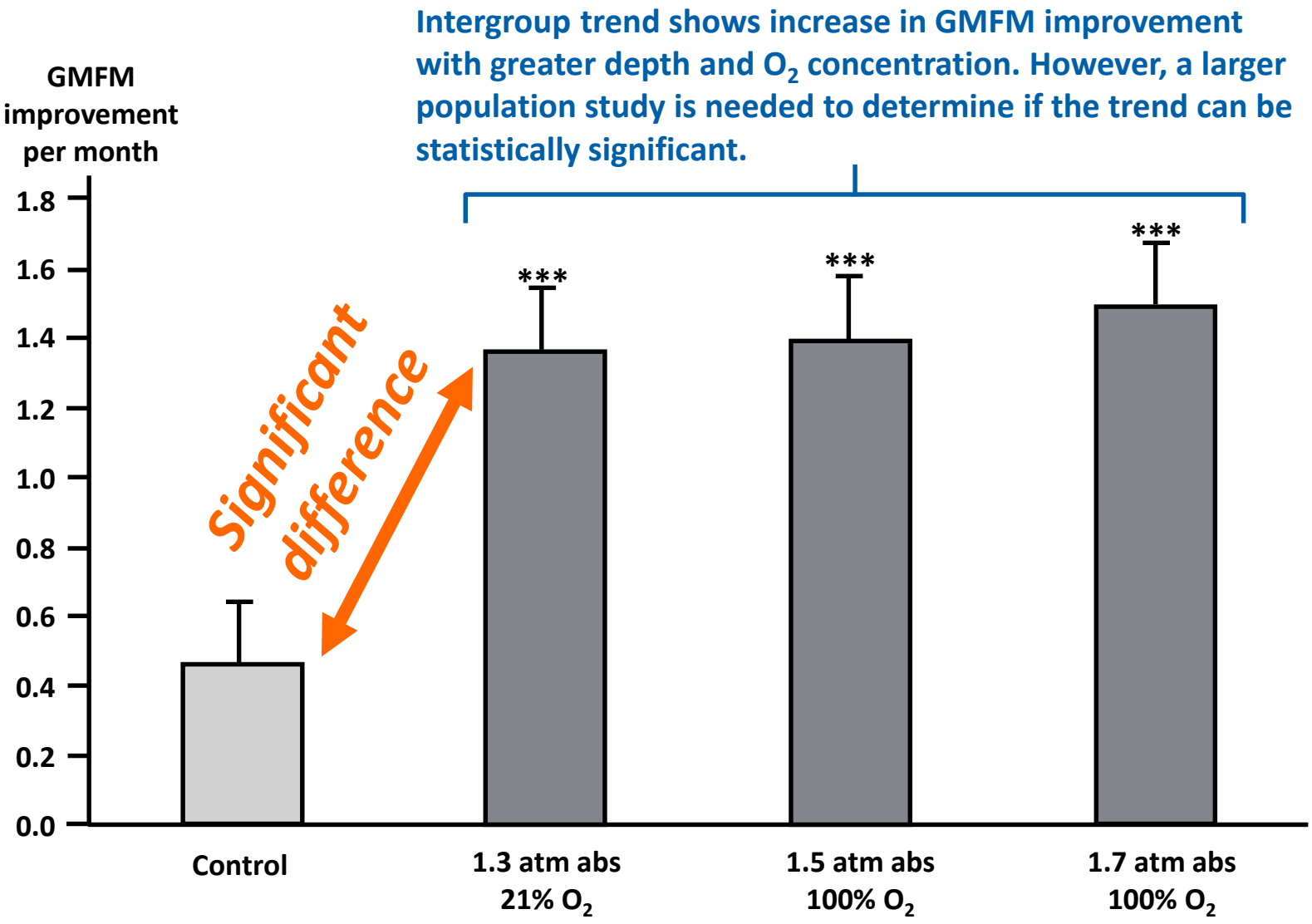
	GMFM observed mean (SD)				
	Before HBOT		4 months after beginning HBOT	6 months after beginning HBOT	
Control	29.6 (13.0)		31.0 (12.8)	32.4 (12.8)	
1.3 ATA 21% O2	29.6 (14.8)		36.2 (13.6)	38.6 (14.3)	
1.5 ATA 100% O2	34.3 (15.6)		39.3 (15.4)	42.5 (15.3)	
1.7 ATA 100% O2	32.5 (11.8)		37.2 (10.8)	42.1 (10.4)	

Table 4: Predicted GMFM from fixed effects models in each group

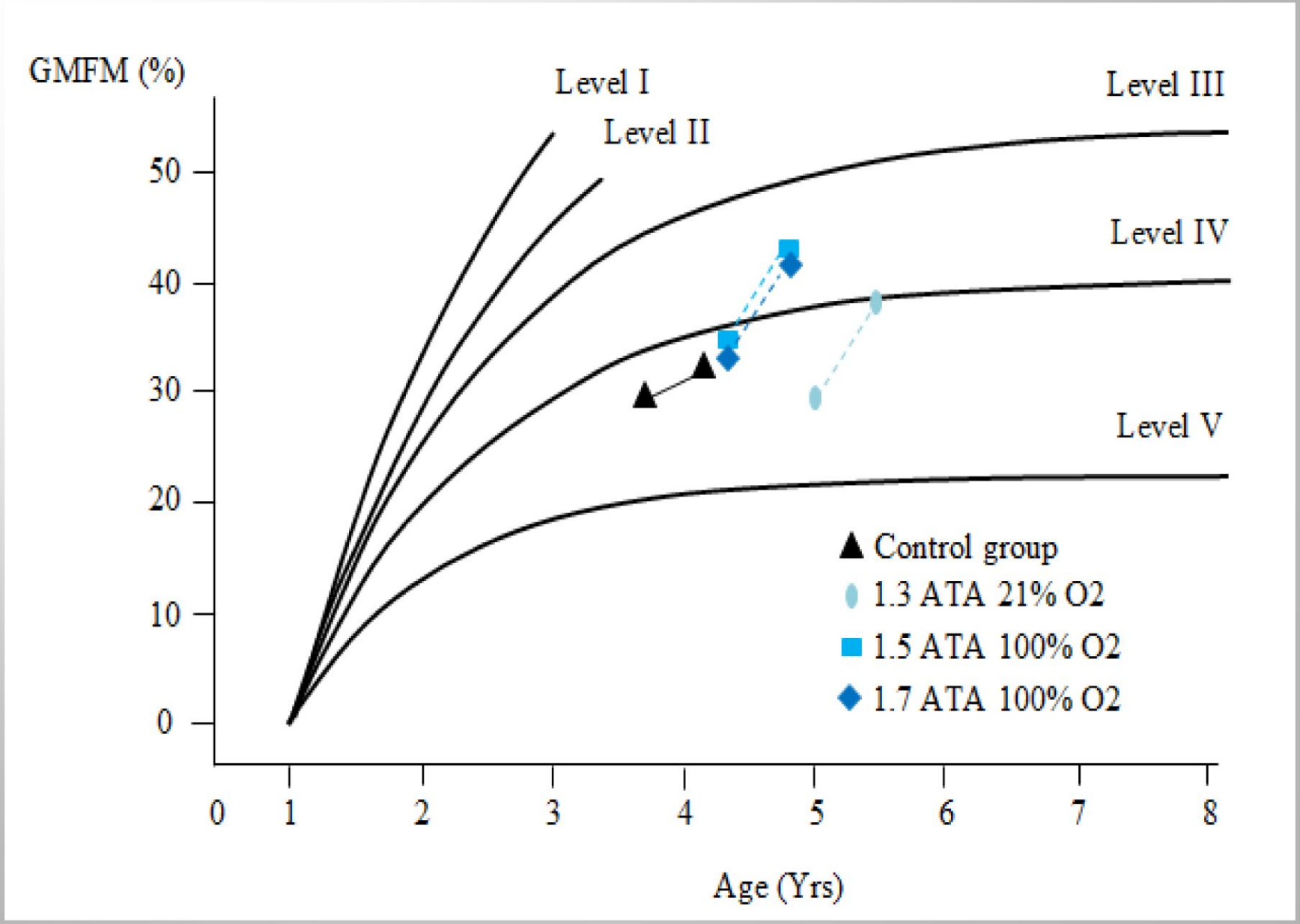
Group	Model
Control group	GMFM = 24.65 + ***0.46 Month*** + 4.96 LnAge
1.3 ATA group	GMFM = 22.75 + ***1.36 Month*** + 4.96 LnAge
1.5 ATA group	GMFM = 27.56 + ***1.40 Month*** + 4.96 LnAge
1.75 ATA group	GMFM = 26.07 + ***1.50 Month*** + 4.96 LnAge

ATM = atmosphere absolute;
GMFM = gross motor function measurement

Fig. 1: Intergroup GMFM Improvement



*** = significantly different from the control group, $p<0.001$; atm abs = atmospheric absolute


GMFM (%)
Level I
Level II
Level III
Level IV
Level V
50
40
30
20
10
0
0
1
2
3
4
5
6
7
8
Age (Yrs)
Control group
1.3 ATA 21% O2
1.5 ATA 100% O2
1.7 ATA 100% O2

This study clearly shows that HBOT, even at mild pressures can have very important effects on the motor function of children with CP.
It finally proves that the beneficial effects observed in The Lancet study and measured in both groups of children of CP treated with two different dosage of HBOT were not due to a placebo effect.

- We now know much more about the physiological mechanisms responsible for the positive effects of HBOT in neurological conditions

HBO2 MECHANISMS IN NEUROLOGICAL CONDITIONS

The important plasmatic increase of O2 concentration combined with the elevated pressure:

-accelerate and improve the cellular repair mechanism
-improve mitochondrial function and cellular metabolism
-improve axonal regeneration and myelinisation
-increases neurolalsticity by reactivating neurons and glials cells in vegetative state
-increases the amount of circulating stems cells
-decreases apoptosis
-increases angiogenesis

Références

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Recents studies with adults

Hyperbaric Oxygen Therapy Can Improve Post Concussion Syndrome Years after Mild Traumatic Brain Injury - Randomized Prospective Trial

Rahav Boussi-Gross1., Haim Golan3,4., Gregori Fishlev1, Yair Bechor1, Olga Volkov3,4, Jacob Bergan1, Mony Friedman1, Dan Hoofien6,7, Nathan Shlamkovitch8, Eshel Ben-Jacob2,5,9,10*, Shai Efrati1,2,3,10*

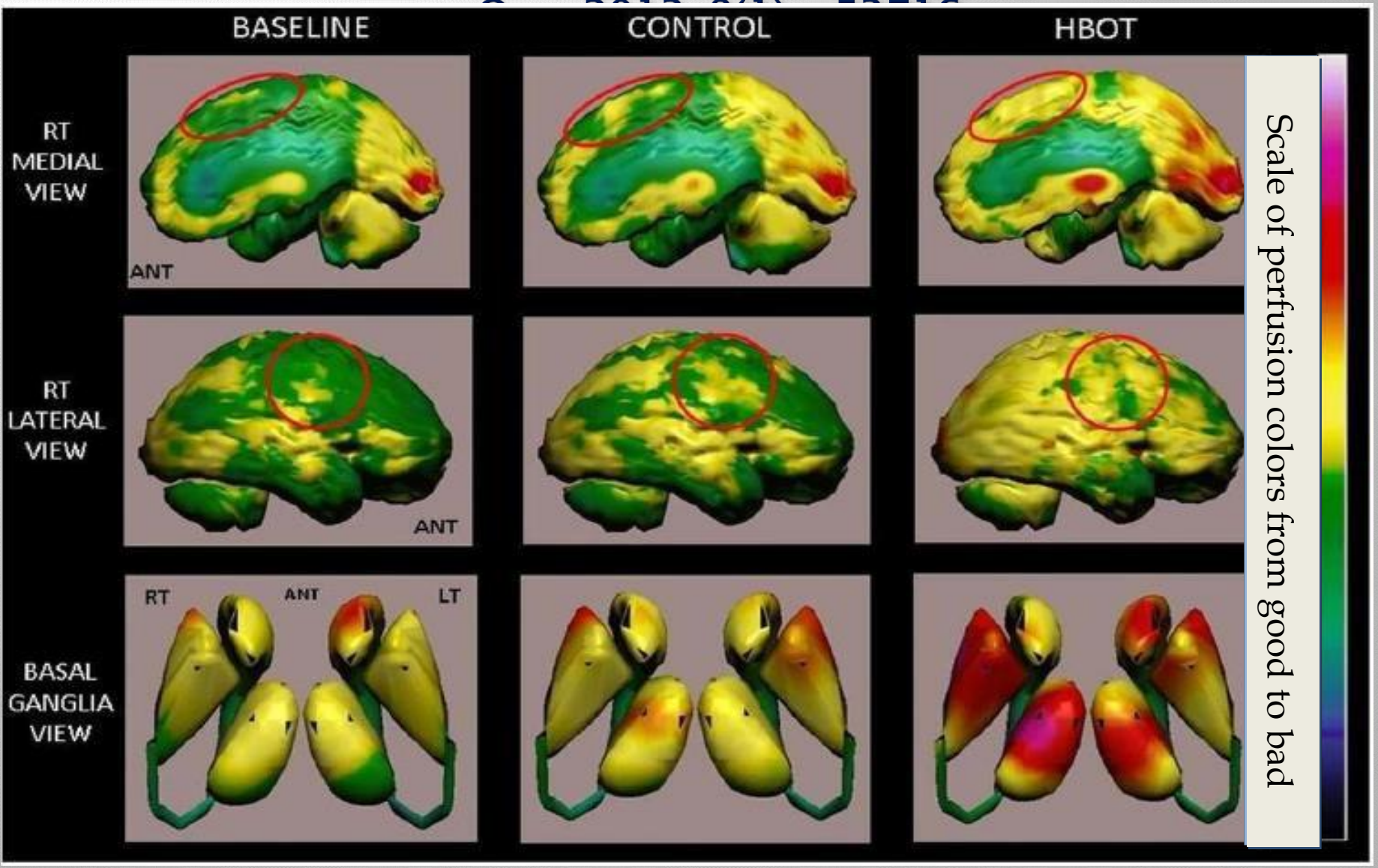
- Conclusions: HBOT can induce neuroplasticity leading to repair of chronically impaired brain functions and improved quality of life in mTBI patients with prolonged PCS at late chronic stage.

Hyperbaric Oxygen Induces Late Neuroplasticity in Post Stroke Patients - Randomized, Prospective Trial

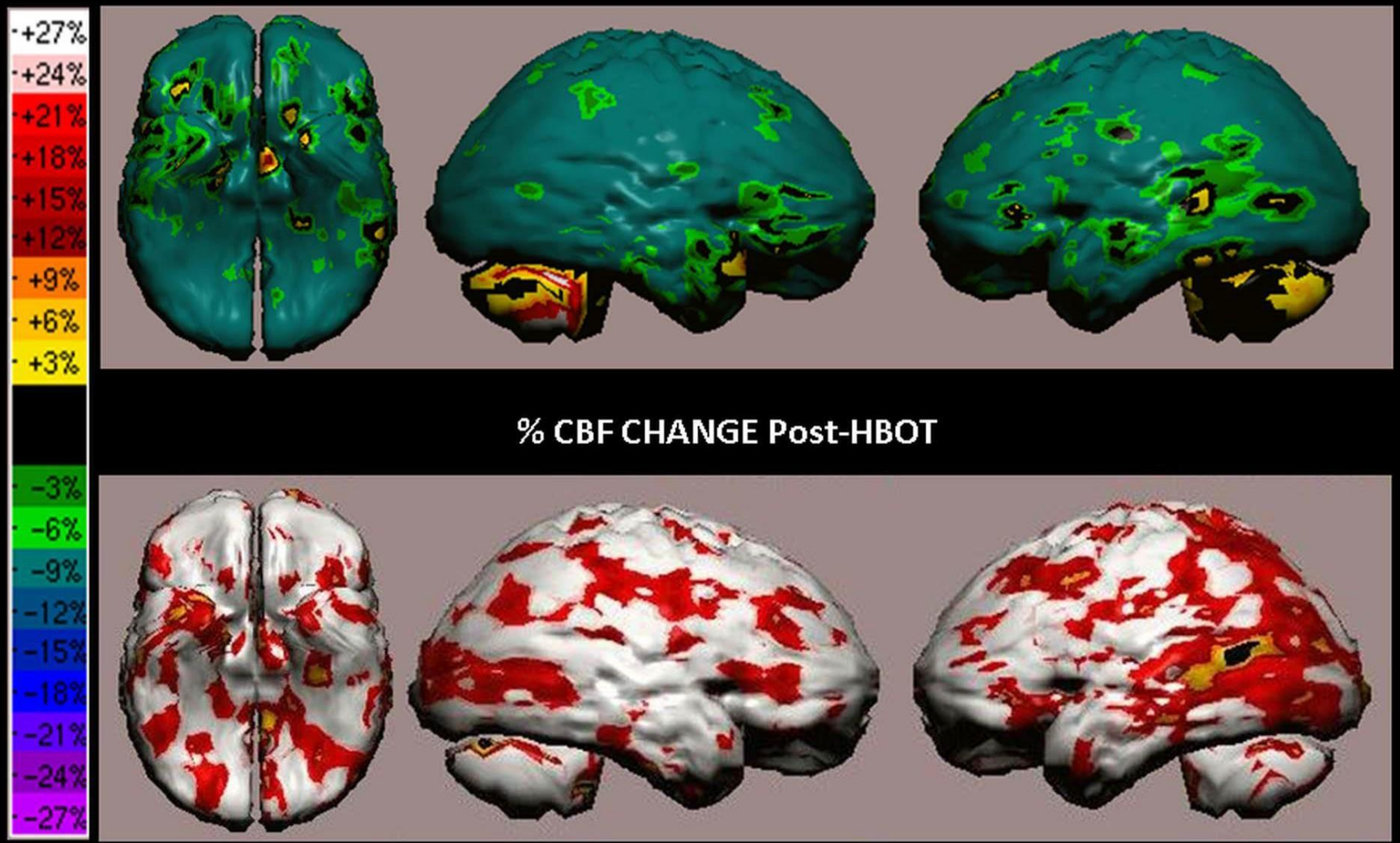
Shai Efrati1,2,3*, Gregori Fishlev1, Yair Bechor1, Olga Volkov3,4, Jacob Bergan1, Kostantin Kliakhandler5, Izhak Kamiager3,6, Nachum Gal1, Mony Friedman1, Eshel Ben-Jacob2,5,7, Haim Golan3,4

- Conclusions: The results indicate that HBOT can lead to significant neurological improvements in post stroke patients even at chronic late stages. The observed clinical improvements imply that neuroplasticity can still be activated long after damage onset in regions where there is a brain SPECT/CT (anatomy/physiology) mismatch.

Efrati S, Fishlev G, Bechor Y, Volkov O, Bergan J, Kliakhandler K, et al. Hyperbaric oxygen induces late neuroplasticity in post stroke patients--randomized, prospectivetrial. PLoS



% CBF CHANGE Post CONTROL



% CBF CHANGE Post-HBOT

Where are we now?

- More than 1000 children with CP treated with HBOT in Quebec alone, 335 involved in studies
- More than 650 children with CP have been treated with HBOT and involved in positive studies conducted around the world and published or presented in international meetings.

What have we learned?

- HBOT gives permanent results in most children with CP.
- About 70% of CP children will have Gross Motor improvements after 40 sessions. Further treatments can lead to more improvement in most cases that have responded to the first 40 sessions.
- Improvements in cognition and communication skills is even more frequent than motor changes.

What have we learned?

- HBOT alone has been shown to produce greater changes in motor function than those obtained with recognized therapies for children with CP.
- HBOT combined to rehabilitation can multiply the effects of standard therapies and vice-versa

What have we learned?

- The period of time between the cerebral damage and the initiation of HBOT does not seem to be an important factor in terms of results…but…the sooner the better, simply because if you can benefit earlier from an improvement in function .. you will exploit it and make it grow with interests!!

What have we learned?

- We have not seen important side effects in more than 100,000 given treatments.
- CP children with epilepsy can be treated with HBOT but the cerebral stimulation induced by HBOT can temporary increase the frequency of seizures.

What have we learned?

- HBOT can have a permanent impact on motor function, cognition, communication thus conducting to improved autonomy, reduction of rehabilitation and personal needs. The need for braces and other equipments, medication and surgeries can often be reduced as well.
- The economical impact can be very important but the most important effects are on the quality of life of children with CP and their whole families.

Conclusion

- Further researches with imagery (SPECT-Scans or PET Scans)are needed to better identify the best candidates and dosages.
- However, considering the very low risks and they the potential permanent benefits of HBOT on most children with CP, we should recommend the use of HBOT combined with recognized therapy for every children with CP.
- Considering the cost effectiveness, it should be covered by health insurances or health care systems.

Thank You!