

The RESCUE BRAIN study :

A French multicenter randomized trial on neuroprotection with lower limb ischaemic per-conditioning in the acute phase of cerebral infarction (<H6)

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Speaker Disclosure

No, nothing to disclose
Yes, please specify:

<i>Company Name</i>	<i>Honoraria/ Expenses</i>	<i>Consulting/ Advisory Board</i>	<i>Funded Research</i>	<i>Royalties/ Patent</i>	<i>Stock Options</i>	<i>Ownership/ Equity Position</i>	<i>Employee</i>	<i>Other (please specify)</i>

The unique source of funding is a grant from the French Ministry of Health (PHRC).

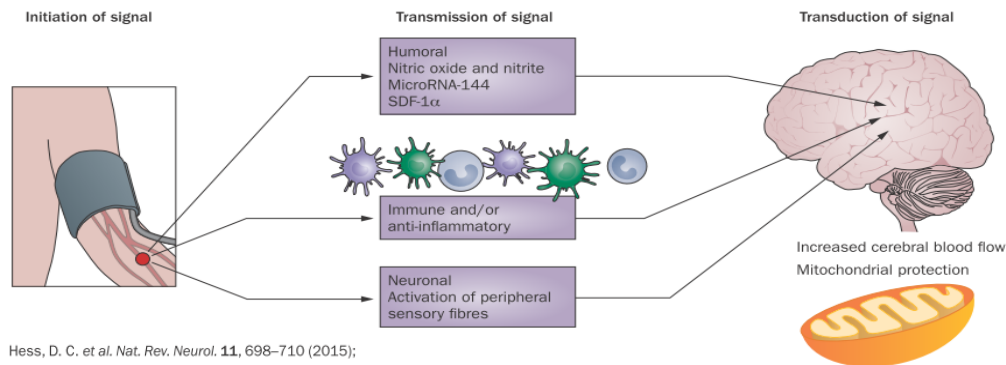
There was no industry funding or involvement in any aspect of the trial



Les Programmes Hospitaliers
de Recherche Clinique
(PHRC)



- There is a need for neuroprotective agent.
- Ischemic conditioning : transient ischemia without necrosis. Endogenous mechanism

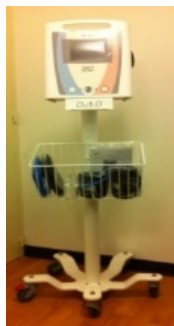


- In good quality preclinical studies in brain infarction (STAIR recommendation) : positive results
 - RPerC effective alone. Additive effect with rTPa in a murine model of embolic stroke (Hoda et al. *Stroke* 2012)
- Promising results in cardiology in myocardial infarction :
 - Botker et al. *Lancet* 2010 , CONDI 2 Large on going trial (n= 5400). No safety issue

To evaluate if remote ischemic Per-Conditionning (RIPerC) in the unaffected lower limb, performed in the first 6 hours of cerebral infarction reduces the growth of the brain infarction

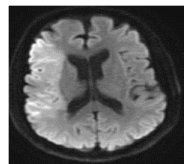
- RESCUE Brain is an interventional, randomized, multicenter trial with PROBE design
- (Prospective Randomized Open, Blinded End-point)
- Source of funding : PHRC IR 2014-A00104-43 (Ministry of Health)
- Approved by the Institutional Review Board (IRB) (Ile de France XI, approval number 14023).
- ClinicalTrials.gov Identifier: NCT02189928
- Design published in Int J Stroke. 2016 Oct;11(8):938-943.
- Randomization has been stratified on the center and on IV thrombolysis.(Draft in 2013)
- Mechanical thrombectomy was allowed following IV thrombolysis (Draft in 2013)
- Interim analysis at half recruitment (n=102 patients)

DESIGN



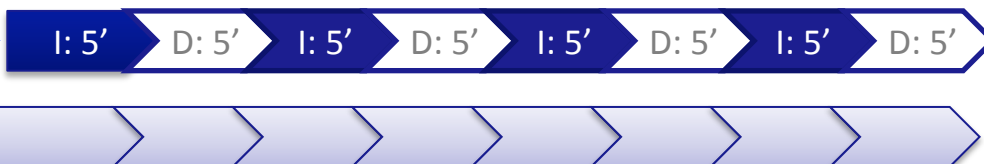
Patients in the intervention group :

- Cuff is placed in the thigh (unaffected side)
- Target inflation BP = 110 mm Hg above syst BP
- Electronic tourniquet is program to deliver
- 4 cycles of 5 min inflation
- With 4 cycles of deflation in between
- Total duration = 40 minutes



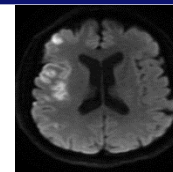
DWI <H6

R



Patients in the Control group :

- The cuff is placed but no inflation



DWI H24
(H24-H36)

- H 24 NIHSS
- D 7 : NIHSS
- M3 : Rankin

Main inclusion criteria:

- patients with carotid BI
- proven by brain MRI < H6
- NIHSS score: 5 and 25.

Primary Endpoint :

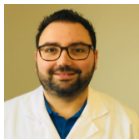
- DWI volume (cc) H24 - Baseline (<H6)
- Central lab for lecture of brain MRI, blinded to clinical data, date of MRI.

RESCUE BRAIN Network

11 French stroke centers (7 in Paris area)



Pr Cordonnier



Dr Ferrigno

Brain MRI



Dr Rosso



Dr Hirel



Dr Ronzière



Dr Guillon



Pr Wolff



Dr Lapergue



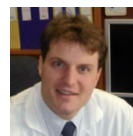
Dr Consoli



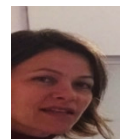
Pr Amarenco



Dr Meseguer



Pr Pico



Dr Chadenat



Dr Piotin



Dr Obadia



Pr Smadja



Pr Hosseini

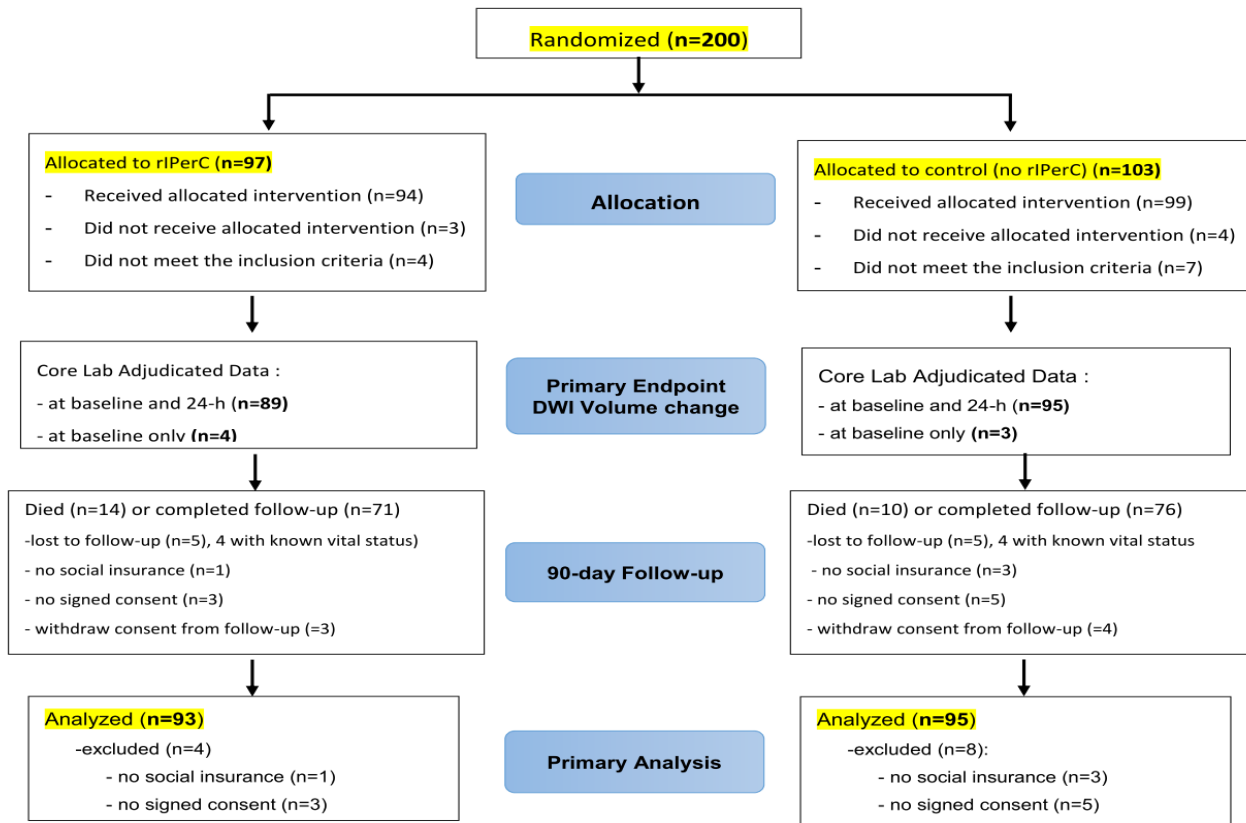


Pr Samson



Dr Deltour

FLOW CHART



BASELINE CHARACTERISTICS

Baseline demographics and medical history	Overall (N=188)	rIPerC (N=93)	Control (N=95)
Age, years, mean (SD)	67.2 (15.7)	67.8 (15.1)	66.7 (16.4)
Men	98/188 (52.1)	45/93 (48.4)	53/95 (55.8)
BMI, Kg/m ² , mean (SD) ¹	26.3 (5.4)	26.2 (5.1)	26.5 (5.8)
Medical history			
Hypertension	98/188 (52.1)	48/93 (51.6)	50/95 (52.6)
Diabetes	30/188 (16.0)	12/93 (12.9)	18/95 (19.0)
Hypercholesterolemia	72/188 (38.3)	32/93 (34.4)	40/95 (42.1)
Current smoking	30/179 (16.8)	14/88 (15.9)	16/91 (17.6)
Coronary artery disease	24/188 (12.8)	12/93 (12.9)	12/95 (12.6)
Previous stroke or TIA	24/188 (12.8)	11/93 (11.8)	13/95 (13.7)
Previous atrial fibrillation	32/188 (17.0)	18/93 (19.4)	14/95 (14.7)

Current stroke event	Overall (N=188)	rIPerC (N=93)	Control (N=95)
Admission NIHSS score, median (IQR)	10 (6 to 16)	9 (6 to 15)	10 (7 to 17)
Onset to baseline MRI time, min, median (IQR)	104 (82 to 145)	105 (81 to 147)	103 (83 to 142)
Occlusion at MRI			
None	59/188 (31.4)	30/93 (32.3)	29/95 (30.5)
MCA	94/188 (50.0)	45/93 (48.4)	49/95 (51.6)
Cervical ICA	6/188 (3.2)	6/93 (6.4)	0/95 (0.0)
Carotid T	11/188 (5.9)	6/93 (6.4)	5/95 (5.3)
Others	18/188 (9.6)	6/93 (6.4)	12/95 (12.6)
Baseline brain infarct volume, cm ³ , median (IQR) ³	11.4 (3.6 to 35.8)	10.2 (3.4 to 38.7)	12.2 (3.7 to 32.3)

Treatments of current stroke event	Overall (N=188)	rIPerC (N=93)	Control (N=95)
IV thrombolysis	164/188 (87.2)	82/93 (88.2)	82/95 (86.3)
Onset to IV thrombolysis time, min, median (IQR)	149 (111 to 179)	154 (111 to 186)	145 (112 to 175)
Endovascular treatment	64/188 (34.0)	30/93 (32.3)	34/95 (35.8)
Onset to groin puncture time, min, median (IQR)	187 (145 to 247)	187 (130 to 250)	182 (150 to 245)
Onset to rIPerC time, min, median (IQR)	-	222 (176 to 275)	-

- **87 % of patients have been treated by I.V. thrombolysis with a median time of 2h30**
- **34% patients have been treated by endovascular treatment with a median time of 3 h10**
- **Concerning rIPerC the median time between stroke onset and cuff inflation was 3 h40.**

PRIMARY ENDPOINT

Brain MRI Volume	rIPerC (n=93)	Control (n=95)	P-Value
ITT analysis			
Baseline, median (IQR)	9.3 (3.4 to 38.3)	12.2 (3.7 to 32.3)	
24-hours, median (IQR)	13.0 (3.2 to 54.7)	18.8 (4.9 to 66.7)	
Mean (\log_e) change (95%CI)	0.30 (0.11 to 0.48)²	0.37 (0.19 to 0.55)	0.57
PP analysis			
Baseline, median (IQR)	9.1 (3.3 to 37.9)	12.1 (3.8 to 32.0)	
24-hours, median (IQR)	13.0 (3.6 to 45.4)	18.5 (4.8 to 60.0)	
Mean (\log_e) change (95%CI)	0.30 (0.12 to 0.49)²	0.33 (0.14 to 0.51)	0.86

SECONDARY ENDPOINT

	riPerC (n=93)	Control (n=95)	P-Value
% change in BI volume at 24-hours, median (IQR) ¹	36.5 (-7.3 to 98.1)	34.1 (-11.0 to 106.4)	0.80
Change NIHSS score at 24-hours			
Baseline, median (IQR)	9 (6 to 15)	10 (7 to 17)	
24-hours, median (IQR)	5 (2 to 9)	7 (2 to 12)	
Mean (log _e) change (95%CI)	-0.59 (-0.75 to -0.43)	-0.51 (-0.67 to -0.35)	0.48
Successful recanalization in IV-treated patients	62 (75.6)	65 (79.5)	0.65
90-day Barthel ≥95	61 (67.2)	56 (61.3)	0.41
90-day mRs 0-1	44 (48.6)	37 (40.3)	0.26
90-day mRs, median (IQR)	2 (1 to 3)	2 (1 to 3)	0.35

	With at least one cycle of deflation/inflation		
	Yes (n=94)	No (n=94)	P-Value
Symptomatic Intracerebral hemorrhage	4/88 (4.6)	4/88 (4.6)	0.97
90-day All-cause mortality, n (%)	14 (15.8)	10 (10.4)	0.45
Pain (VAS) during per-conditioning ischemic procedure			
>0	41/78 (52.6)	-	-
Median (IQR)	6 (3 to 7)	-	-
(Data reported for only for patients with VAS>0)			

PerCID related event :

- No acute limb ischemia
- No deep venous thrombosis

DISCUSSION

- Previous RCT on rIPerC in acute Stroke (KD Hougaard et al. Stroke 2014) G Andersen, Aarhus University Denmark
 - Prehospital setting : 64 and 57 patients analyzed with post rIPerC MRI (DWI and PWI)
 - Low NIHSS = 4 and small volume 1 cc.
 - Neutral but post hoc voxel analyses suggest rIPerC can be beneficial

- 5 on going trial on rIPerC in AIS : 2 in Prehospital and 3 with multiple cycle of per CID

Name	Country (PI)	n	Patients	Intervention	Intervention	Outcomes
RESIST	Denmark (R A Blauenfeldt)	1500	AIS HIC	<ul style="list-style-type: none"> • PreHosp • Non paretic Arm 	<ul style="list-style-type: none"> • InHosp H6 • D1-D7 = *2/d 	mRS 2022
REMOTE-CAT	Spain,Catalonia (F Purroy Garcia)	575	AIS	<ul style="list-style-type: none"> • PreHosp < H8 • Non paretic Arm 	<ul style="list-style-type: none"> • Once 	mRS 2022
RE CAST-2	United Kingdom (T England)	120	AIS	<ul style="list-style-type: none"> • In Hosp • Non paretic arm 	<ul style="list-style-type: none"> • D1-D4*2/d 	Feasibility 2018
TRIPCAIS	China (A Jiaqi)	120	AIS rTPA	<ul style="list-style-type: none"> • In Hosp • Non paretic arm 	<ul style="list-style-type: none"> • Once after IV thrombolysis 	2020
REPOST	Netherlands (T Landman)	200	AIS	<ul style="list-style-type: none"> • In Hosp • Non paretic arm 	<ul style="list-style-type: none"> • Twile daily 	Infarct size

CONCLUSION

RESCUE BRAIN is a neutral RCT evaluating
in hospital remote ischemic per conditioning at lower limb
within the 6 first hours of proven ischemic stroke
on top on IV thrombolysis and mechanical thrombectomy

Acknowledgements

Patients and their families

Center (number of patients included)

VERSAILLES HOSPITAL (n=48) Pr PICO, Dr CHADENAT, Dr DUONG et al.
 FOCH HOSPITAL (n=42) Dr LAPERGUE, Dr BOURDAIN, Dr CONSOLI, et al.
 LILLE HOSPITAL (n=28) Pr CORDONNIER, Dr FERRIGNO et al.
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 MONDOR APHP (n=5) Pr HOSSEINI, Dr MAJHAI et al.
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 RENNES HOSPITAL (n=0) Dr RONZIERE et al.

BRAIN MRI Lecture group :

- Dr C ROSSO (BRAIN AND SPINE INSTITUTE)
- Dr C HIREL (VERSAILLES HOSPITAL)

VERSAILLES CLINICAL RESEARCH UNIT :

- Ms MORISSET
- Ms CATTENOY , Ms ROUX
- Ms LEFEVRE, Mr TURBE

PARIS OUEST CLINICAL RESEARCH UNIT

- Pr AEGERTER (Methodologist)
- Ms AZERAD (Data Manager)
- Ms NKAM (Statistician)

DSMB:

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- Pr OLIVOT (Toulouse)
- Ms COZIC (Paris)

LILLE BIOSTATISTIC DEPARTMENT

- Pr DUHAMEL
- Mr LABREUCHE(Statistician)