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**Quatre semaines de programme quotidien
d'entraînement par intervalles avec récupération active
pour améliorer la marche chez l'artériopathe claudicant :
essai clinique randomisé**

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**QUATRE SEMAINES DE PROGRAMME QUOTIDIEN
D'ENTRAINEMENT PAR INTERVALLES AVEC
RECUPERATION ACTIVE POUR AMELIORER LA
MARCHE CHEZ L'ARTERIOPATHE CLAUDICANT :
ESSAI CLINIQUE RANDOMISE.**

THESE
PRESENTEE POUR L'OBTENTION DU DOCTORAT EN MEDECINE
DIPLOME D'ETAT

Valérie THOREAU
Née le 29/07/1986 à Rennes (35)

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Directeur de Thèse : Me le Docteur Béatrice VILLEMUR

*«La motivation vous fait commencer,
mais c'est l'habitude qui vous fait continuer.»*

Jim Ryun

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Abstract

FOUR-WEEK DAILY PROGRAM OF INTERVAL TRAINING WITH ACTIVE RECOVERY FOR IMPROVING GAIT IN VASCULAR CLAUDICATION: RANDOMIZED CLINICAL TRIAL

Background – Supervised exercise training is part of the first line therapies for patients with intermittent claudication (IC), however the content of the gait training remains to be determined. Treadmill training with active recovery has been proven efficient in cardiac rehabilitation. This monocentric trial was aimed at testing treadmill training with active recovery as a novel rehabilitation approach for IC.

Methods and Results - Forty patients were randomized to either interval training with active recovery (ITAR) or interval training with complete rest (ITCR) program, 3 hours a day, for 4 weeks. The primary outcome measure was maximum walking distance (MWD) measured with a graded treadmill test before and after program.

Adherence was high in both groups (>95%), and tolerance excellent (no adverse event). In the two groups, walking abilities were as much improved as with six-month programs, 3 days a week. The intensity and the energy expenditure of training were lower in the ITAR than in ITCR. ITAR program was similar to ITCR program in improving the maximum walking distance measured with a graded treadmill test and a Strandness test, and in changing the peak oxygen uptake. ITAR program appeared effective in increasing the perception in walking speed, but not ITCR.

Conclusions

The interval training with active recovery might be of interest for PAD patients limited by IC at high cardiovascular risk, due to the lower intensity of the training, and for patients available for a short period of time (one month).

Keys Words: peripheral arterial disease, rehabilitation, exercise physiology, treadmill training with active recovery

Résumé

QUATRE SEMAINES DE PROGRAMME QUOTIDIEN D'ENTRAÎNEMENT PAR INTERVALLES AVEC RECUPERATION ACTIVE POUR AMELIORER LA MARCHE CHEZ L'ARTERIOPATHIE CLAUDICANT: ESSAI CLINIQUE RANDOMISE

Contexte – Les exercices physiques supervisés font partis des traitements de première intention chez les patients souffrants d'une claudication intermittente (CI). Mais le contenu reste à déterminer. Un réentraînement sur tapis roulant avec récupération active est efficace dans la réadaptation cardiaque. Cet essai clinique monocentrique visait à évaluer un réentraînement sur tapis roulant avec récupération active comme une nouvelle approche de réadaptation chez les patients claudicants.

Méthode et Résultats – 40 patients ont été randomisés pour réaliser un entraînement par intervalles soit avec une récupération active (EIRA) soit avec un repos complet (EIRC), 3 h/jr, durant 4 semaines. Le critère de jugement principal était la distance de marche maximale mesurée par un test graduel sur tapis roulant, réalisé avant et après rééducation.

L'observance a été élevée dans les deux groupes (>95%), et la tolérance excellente. Dans les deux groupes, l'amélioration des capacités de marche a été similaire à celle retrouvée dans des programmes de six mois, trois jours par semaine. L'intensité du réentraînement, et la dépense énergétique globale étaient plus faibles dans le groupe EIRA que dans le groupe EIRC. Le programme EIRA était similaire au programme EIRC pour : l'amélioration de la distance de marche mesurée avec un test graduel et un test de Strandness, et pour la variation de la consommation pic d'oxygène. Le programme EIRA semble efficace pour augmenter la perception de la vitesse de marche (Walking Impairment Questionnaire), mais pas l'ITCR.

Conclusions – L'EIRA pourrait être intéressant chez le patient avec CI, à haut risque cardiovasculaire, en raison de la faible intensité du réentraînement, et sa durée courte.

Mots-clés : artériopathie des membres inférieurs, rééducation, physiologie de l'exercice, réentraînement avec récupération active.

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INTRODUCTION

Peripheral arterial disease (PAD) with intermittent claudication affects 0.8 to 1.5% of the general population (1), which limits their walking ability, and their physical activity levels when compared to non-PAD patients (2)(3). These patients have twice the ten-year risk of total mortality, cardiovascular mortality, and major coronary events at all levels as displayed by the Framingham risk factor (4). Thus, improving functional status in patients with PAD is a great challenge. Both, revascularization and exercise training are effective (5). According to international guidelines as a Class I recommendation by the American College of Cardiology and the American Heart Association (6), the American Association of Cardiovascular and Pulmonary Rehabilitation (7), the American College of Sports Medicine (ACSM) (8), the French Health Authority (9), patients with intermittent claudication should receive an initial medical treatment with the management of cardiovascular risk factors, lifestyle coaching and supervised exercise therapy (10). A recent systematic review (11) showed that exercise training performed by patients were varied : mainly walking treadmill programs but also different ergometers like lower limb or arm cycling, and plantar flexion. Exercise therapy on treadmills was first explored in the 60th (12)(13). These programs, have further been proven efficient (14)(15)(16)(10)(17). The benefits are attributed to muscle metabolic and microcirculatory adaptations as well as improvement of cardiorespiratory fitness and quality of life (18)(19)(20)(21). Moreover, these methods also help to reduce cardiovascular risk by lowering blood pressure and improving glucose and lipid metabolisms (22)(23). It is usually recommended for a patient to undergo supervised intermittent treadmill walking at an intensity close to the maximal claudication pain, at least three times per week (24)(21). A complete rest is recommended between walking periods.

In a recent pilot study (25), we performed a novel treadmill exercise program for 11 patients with claudication based on interval training with active recovery. Patients improved their walking distance with a good overall tolerance and observance. This type of program has long been used mainly in patients with chronic obstructive pulmonary diseases (26). Moreover, this program use of interval training was found more efficient in improving cardiorespiratory fitness and metabolic syndrome (27) than a standard program of exercise (distributing a

continual not interval intensity) in patients who underwent a coronary artery bypass surgery (28)(29) or that experienced heart failure (29). Tolerance was sufficient, even in subjects with a very altered heart rate (30). This rehabilitation with interval training is now recommended during cardiac rehabilitation in patients with severely diminished functional capacity (31). For PAD patients, one could expect that interval training with active recovery program will be more efficient because i) active recovery seems more effective on lactate removal curve (32) and, at low intensity, to recover the metabolic state of muscle (33), ii) patients do not walk up to the pain which could increase tolerance iii) walking intensity during active recovery periods is low, which could improve walking abilities of PAD patients for moderate exercises, corresponding more to daily activities.

Rehabilitation programs lasted most often 6 weeks to 6 months (11). For patients still in work the shortest duration of an efficient rehabilitation program could be a great challenge. Also, reduce the length of hospital rehabilitation program would reduce the cost of care for each patient and, increase the number of patients cared for every year.

The purpose of this randomized trial was to compare the efficiency of two different daily rehabilitation programs, lasted four weeks: interval training with active recovery (ITAR) versus interval training with complete rest (ITCR) (constant slope and constant speed, rest recovery if necessary). The primary outcome was maximum walking distance (MWD) measured with a graded treadmill test before and after program. The secondary outcome measures were hemodynamic, cardiorespiratory, walking impairment questionnaire (WIQ) and hospital anxiety and depression scale (HADS) questionnaires.

METHODS

Ethics

The study was approved by the regional medical research ethics committee (N° 2011 A00969-32) and declared to clinicaltrial.gov data base trials (N° NCT01734603). Written informed consent was obtained from all patients.

Randomization

The randomization procedure was centralized, and performed using a computer random number generator to select block size random. Subjects were included after initial assessments, then randomly assigned to either program.

Blind

In rehabilitation program a double-blind trial is not feasible, then we realized a single blind trial: subjects were aware of the treatment but the staff was not. For some patients, for reasons of staff available, we were unable to complete blind assessments by physiotherapist.

Sample size

To demonstrate a difference in walking distance of 350 m with a standard deviation of 350 m (corresponding to the data of the pilot study) at a power of 80% and an alpha risk of 5%, 18 patients per group had to be enrolled, 36 patients in total. We planned to include 10% more patients to anticipate patients who do not achieve all rehabilitation sessions.

Inclusion criteria

The inclusion criteria for participation in the study were: patients between 18 and 80 years with claudication secondary to arterial insufficiency investigated by a trained vascular

physician an ankle–brachial index (ABI) < 0.9 at rest and a 20 % decrease in ABI after the constant treadmill test (C-test). Exclusionary criteria were: exercise tolerance limited by factors other than claudication (poorly controlled blood pressure, coronary artery disease, dyspnea, severe osteoarticular or neurological impairments), abdominal aortic aneurysm with diameter > 40 mm, medical instability. Each participating patients' conditions were checked by the patient's cardiologist and vascular physician less than three months before inclusion. The preinclusion tests involved an assessment of cardiovascular risks, a duplex ultrasound, and a graded cycling cardiac exercise test. Other exclusionary criteria included: court granted exemption or other administrative or legal protectionary measures.

Patients

Among the 60 patients screened, 40 were enrolled from October 2012 to April 2014 (see flow-chart in figure 1). Two patients were excluded from the study after randomization: one due to a cardiac disease revealed by walking tests on the first day, one for repeated alcohol abuse. The remaining data analyzed were those of the 38 patients who completed the study, 18 in the group participated in ITCR, 20 patients in the group underwent ITAR. The patients' characteristics are given in table 1 and table 2.

Rehabilitation programs

All patients, in both groups, followed a four-week daily rehabilitation program (17 days of training), 3 hours a day, and undertook treadmill training (ITCR or ITAR) and an exercise program (global gym, home cycling, arm cycling). For the treadmill training the warm-up and the cool-down lasted five minutes each. The training intensity was incremented at each session if it was successful, either by increasing the treadmill slope or the speed. The treadmill training was performed on a treadmill (TechmedPhysio^R) allowing precise speed and slope adjustments (speed accuracy of 0,06 mph, and slope accuracy of 0,5%). The program was supervised by exercise physiotherapists.

Patients participating in the program also benefitted by receiving therapeutic education on

managing cardiovascular risk factors. Their regular drug treatment remained unchanged during the study.

The only difference between the two groups was in the treadmill training. Patients conventionally trained by ITCR walked at a constant speed defined for a given session, with a resting period allowed in case of pain. Patients trained by ITAR alternated between two different walking speeds, one speed for the training period and a second slower pace for the recovery period. The detail of the two training programs are presented below.

Interval training with complete rest (ITCR)

The protocol for ITCR program was based on a proposal by Hiatt (20). Each treadmill session lasted 50 minutes including 5 minutes warm up, 40 minutes of intermittent exercise at constant speed and slope, then 5 minutes cool-down activities. The initial speed was 2 mph with a 0% slope. 11 Patients unable to walk at this speed started at 1 mph with a 0% slope. The training intensity was increased the next session if the patient was able to walk at least 8 minutes. The increasing of the intensity is presented in annex 1. If patients had a severe claudication pain (> 3 on ACSM claudication pain rating scale) (34), they stopped walking until all pain disappeared. They began walking again as soon as possible, according to the recommendations (21).

Interval training with active recovery (ITAR)

Each session lasted 40 minutes and constituted of 5 cycles of 6 minutes, combining 3 minutes of walking at the targeted intensity followed by 3 minutes of active recovery and warm-up and cool-down activities.

During the first session, the walking speed was initiated according to maximum speed achieved during the baseline maximal treadmill test. The speed for the workout was set at 70 % and the speed for the active recovery was set at 40%. If the session was successfully

achieved (patients didn't fall a claudication during the training session), then the intensity was incremented at the next session. The improvement of the training difficulty is presented in the annex 2.

Assessment

All patients were assessed at the beginning (Day 0 and Day 1) and at the end (Day 25 and 26) of the program: a set of cardiovascular, respiratory, walking distance and psychological parameters was collected, in addition to general medical data.

1. The *primary outcome* was the maximum walking distance, in absolute value, measured using a graded treadmill test (G-test), derived from the Gardner-test (35), with a lower slope increment. We hypothesized, as in clinical trial conducted by Nicolai (35), that a slower increase in workload might make the test easier in severe patients able to perform a very limited walking distance. The graded exercise test was performed on a treadmill (TechmedPhysio^R), starting at 2 mph and 0% grade. Then, the slope was increased by 0.5 % (versus 2% for Gardner) every 2 minutes until pain limitation, with a constant speed.
2. The *secondary outcomes*: maximum claudication distance was measured during a constant treadmill test (C-test), while ankle-brachial index (ABI) was measured before and after test, and Visual Analog Scale (VAS) at the end of C-test. Walking distance was assessed by the six-minute walk test (6MWT). Peak oxygen consumption was measured during a third graded treadmill exercise test (V-test), with assessment of transcutaneous oxygen pressure prior. Walking disability was assessed with the WIQ, and anxiety and depression with the HADS.

Walking Distance tests

Maximum walking distance was assessed by the six-minute walk test (6MWT) (36), the constant treadmill test (C-test) proposed by Strandness (2 mph on a 10% slope) (37) and the G-test, systematically in this order.

As suggested by Gardner for PAD patients (38), the 6MWT was performed after 15 minutes of resting. Patients had to walk indoor on the floor at comfortable speed for six minutes.

The C-test was performed on a treadmill (TechmedPhysio^R). Handrail support was allowed during each treadmill test if necessary. ABI (39) was obtained from the more severely diseased lower extremity by the Doppler ultrasound technique before (at rest) and after (1-3 min) the C-test.

Aerobic capacity and walking economy

Cardiovascular, metabolic and respiratory parameters were measured during a graded exercise test on a treadmill (V-test) (Gymrol Super 2500, Tecmachine SA, Andrezieux-Boutheon, France). The initial speed was 1,5 mph with no slope. The speed or the slope were increased every 2 minutes until pain limitation or exhaustion, respectively 2% and 0,5 mph.

Heart rate was monitored continuously with a 12-lead electrocardiogram (ECT WS 2000, CardiolineTM, Remco, Italy). Gas exchanges were measured continuously on an automated ergospirometer using a mixing chamber method (Metasys TRM, BrainwareTM, Toulon, France), allowing monitoring of oxygen uptake (VO_2), carbon dioxide output (VCO_2) and ventilation (V_E). To evaluate the walking economy, the VO_2 was measured during the first minute of the treadmill test before and after the training (11). To determine lactate kinetic, an arterialized blood sample taken from a fingertip was assessed during the last 30 seconds of each stage of exercise to determine lactate kinetic. Blood lactate was measured by an enzymatic method and revealed by spectrophotometry (Nova, USA). The first lactate threshold was determined with a graphic method using three experimented observers as recommended by the French society of Sports medicine (40).

The pain usually perceived by the patients was assessed with a visual analogical scale (VAS) at the end of each stage of exercise. The score ranged between 0 and 10

centimetres.

Estimation of energy expenditure during training

As proposed by Gardner (41), oxygen uptake during walking was estimated using the following equation from the ACSM: $VO_2 \text{ (mL.kg}^{-1}\text{.min}^{-1}) = 3,5 + (0,1 \times \text{speed [m/min]}) + (1,8 \times \text{speed [m/min]} \times \text{slope})$ (8). Metabolic equivalents (METS) were calculated by devising oxygen uptake value by 3,5. The energy expenditure of training was calculated by multiplying the MET value by the duration of exercise sessions, then multiplying by the number of sessions carried.

Intensity of each exercise training session was determined by devising the oxygen uptake value by the VO_2 peak, measured during the baseline maximal treadmill test. We have calculated equally the intensity compared to the predicted VO_2 (VO_2 pred). The predicted VO_2 was calculated by the Wasserman's equation on ergocycle (42). The result was multiplied by 1,1 to obtain VO_2 pred on a treadmill as recommended (43).

Transcutaneous oxygen pressure (TcPO₂)

TcPO₂, measured at rest, is a non-invasive method of partial pressure of oxygen measure on the foot skin surface, giving a direct indication onto the microcirculatory function (10). Foot TcPO₂ values were obtained with a Clark-type polarographic electrode heated to 45°C to induce maximal vasodilatation of the dermal capillaries. The electrode was calibrated to the partial pressure of oxygen (PO₂) present in room air, and was placed on the dorsum of the foot over the third cuneiform bone. The measure was made in stable hemodynamic conditions (after a supine position strict rest of thirty minutes). TcPO₂ values were those of the most severely diseased lower limb.

Walking Impairment Questionnaire

The WIQ assesses specifically the functional disability for patients with PAD (with especially an evaluation of walking distance, walking speed and stairs-climbing abilities) (44)(10).

Hospital Anxiety and Depression Scale

The level of anxiety and depression was assessed using the HADS questionnaire (45) (46), an ordinal scale well suited to PAD patients and often used in this context (31).

Safety

All patients were seen daily by doctors during their rehabilitation, to ensure the good tolerance of program, and detect an adverse event.

Statistical analysis

Adherence was calculated as total number of sessions attended / total number of sessions available x 100. Statistical analysis was performed after the usual procedures of data management and data freezing through the Stata Version 13.0 (Stata Corp., College Station, Texas) software under OSX. Statistical tests were performed with the risk of error first common species alpha equal to 0,05. We used data to describe the numbers and percentages for categorical variables, and medians and interquartile range (IQR) [25th and 75th percentiles] for continuous variables. A table with the baseline characteristics of patients of the two randomized groups is presented without statistical test according to the practice because it was a randomized study. For quantitative variables, we used the Mann-Whitney test to compare the two groups (nonparametric test

RESULTS

Adherence to the two programs was excellent during the entire study (table 3). No adverse event was found in relation to the training. The average duration of each session, and, the intensity and the energy expenditure of the training were lower in the ITAR than in the ITPR program (Table 3). All patients in ITAR program performed successfully all the training sessions, with no stop, whereas only 3 patients in ITCR program.

Baseline data are presented in figure 2, figure 3, table 4 and 5.

Maximum walking distance, evaluated with the G-test, was 415 metres for patients in ITCR group and 400 metres in ITAR group. VO₂ peak was low in both groups (ITCR: 18,2 mL/kg/min versus ITAR: 17,9 mL/kg/min), and most patients had exercise intolerance due to pain limitation, regardless of the group (VAS at the final level, ITCR: 8.2 [7.5-10] and ITAR: 8.5 [7-10]). HADS scores revealed no anxiety or depression.

Changes after rehabilitation

Main outcome criteria (Figure 2). The improvement of the maximal walking distance measured with the G-test was not significantly different between groups.

Secondary criterias (Table 4, 5 and figure 3).

Walking distances

There was no significant difference in maximal walking distance assessed with the C-test between the ITCR and the ITAR group. The distance walked during the 6MWT was not significantly different between groups. The decrease in time to relief of claudication pain was not different between groups.

There was no significant difference in the magnitude of change of ABI at rest and after the treadmill test between ITCR and ITAR program.

Exercise tolerance. After four weeks of exercise training, there was no significant difference between the two groups in change of VO₂ peak. The change of the VO₂ measured at the first minute of the V-test was not different in the two groups. The decrease of pain, evaluated with the VAS, was statistically more important for the first level in ITAR group, but there was no significant difference for the level 2 and 3.

Transcutaneous oxygen pressure. The decrease of TcPO₂ values was not significantly different between ITCR group and ITAR group after the rehabilitation.

Patients' perception of walking abilities. There was a significant difference in the change of WIQ walking speed score after the 4-week rehabilitation program in favor of the ITAR program. This meant that patients trained with the active recovery program felt being able to walk faster after 4 weeks of training. No other significant difference was found between the two groups regarding other WIQ scores.

Anxiety and depression. There was no significant difference between groups after the training program for anxiety score and depression score.

DISCUSSION

This is the first randomized trial to evaluate the efficiency of a four-week daily rehabilitation program.

The improvement of MWD obtained during this four-week program was similar to that obtained in previous trials with six months of rehabilitation (14)(47)(48)(49)(50) : walking distance measured with a G-test was increased by 315 meters (88,5%) in ITCR group and 480 meters (98,5%) in ITAR group, and, with a C-test, increased by 110 meters (85,7%) in ITCR group and 130 meters in ITAR group (71,7%). Gardner has already demonstrated that gains in MWD occur rapidly within the first two months of exercise rehabilitation (51). Moreover this rehabilitation program (ITCR or ITAR program) is safely (no adverse events) adequate to improve maximum walking distance with a high rate adherence (> 95%). The high adherence, greater than that reported in previous randomized exercise trial for PAD patients with claudication, can be explained by a daily and a short duration of one month rehabilitation program (52)(47)(50)(53). A previous trial showed that, during a 6-month rehabilitation program, exercise adherence progressively declined from the first two months to the final two months (51). Additionally, no adverse events have been occurred during the rehabilitation program. However, PAD patients frequently have co-existent coronary artery disease, so each patient was evaluated by a cardiologist in the previous six months to identify potential cardiovascular complication. More over 4-week programs seem easier compatible with patients still work, and less expensive for each patient.

This is the first randomized trial assessing the efficiency of interval treadmill training with active recovery program for PAD patients. The major finding of this study was that PAD patients with claudication, who completed ITAR program, had similar improvements in physical function as those patients who completed ITCR program. Included patients performed a complete training program comprising, for each three-hour session, a treadmill training (ITCR or ITAR) and an exercise program similar for the two groups (global gym, home cycling, arm cycling). The treadmill training represented one third of a daily rehabilitation session, that explained may be the no difference between the two treadmill trainings. Indeed, exercises performed during the common part of the two programs were also efficient to increase aerobic capacity and walking abilities in PAD patients (11).

Intensity and energy expenditure of training were significantly lower in the ITAR group than in the ITCR group, with shorter sessions. These findings suggest that exercise performed even at low intensity can improve these functional measures, which may lower the risk for subsequent morbidity and mortality (54).

However, ITAR seems effective in improving the perception of walking speed, but the ITCR program seems not. The ITAR program could decrease more the pain of claudication for low speeds, and without slope, which correspond more to daily activities. Indeed, the decrease of VAS was significantly more important in ITAR group than ITCR group for the first level of the treadmill test (V-test) and close to significant for the second level. The small sample of patients in this study may explain the lack of significant results for the different levels, except the first one, of submaximal exercise. Addition, informal comments from that patients in ITAR group found it motivating to have a varied procedure to follow during each session, whereas those in the ITCR group found it “quite boring” to walk continuously during the entire exercise period, if they were not stopped by claudication. And, patients in ITAR group performed successfully all the training sessions, with no stop; we can expect that ITAR program was better tolerated than ITCR program, and was most suitable for walking ability of each patient.

Limits

Although the results of this trial support the efficiency of the two 4-week exercise rehabilitation programs for PAD patients, several limitations exist:

Primarily, patient’s assessments were performed blindly, with the exception of walking tests for some patients, for reasons of physiotherapists not available.

Secondly, we have reached the required number of subjects to be included in the deadline, however, the small sample and the short duration of the rehabilitation programs explain may be some no significant results for the secondary outcomes. As part of the ARTEX study, we also planned to review all patients at one year of the end of rehabilitation to assess whether the benefits of rehabilitation are maintained.

CONCLUSION

Our study showed the high adherence and tolerance of a daily program (3 hours a day during four weeks) of rehabilitation dedicated to PAD patients with claudication. Interestingly, walking abilities were as much improved as with 6-month programs, 3 days a week, well described in the literature. Two treadmill trainings were assessed. As compared to the conventional interval training with complete rest when patients experienced pain, a novel program of interval training with active recovery (lower cost of energy expenditure) better improved patients' perception of walking speed, and similarly improved the maximal walking distances on a treadmill (G-test and Strandness test). The interval training with active recovery might be of interest for patients at high cardiovascular risk, due to the lower intensity of the training, and for patients available for a short period of time (one month). A follow up of this cohort of patients will investigate the possible long-term beneficial effects of these programs.

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram of patients through each stage of the trial.

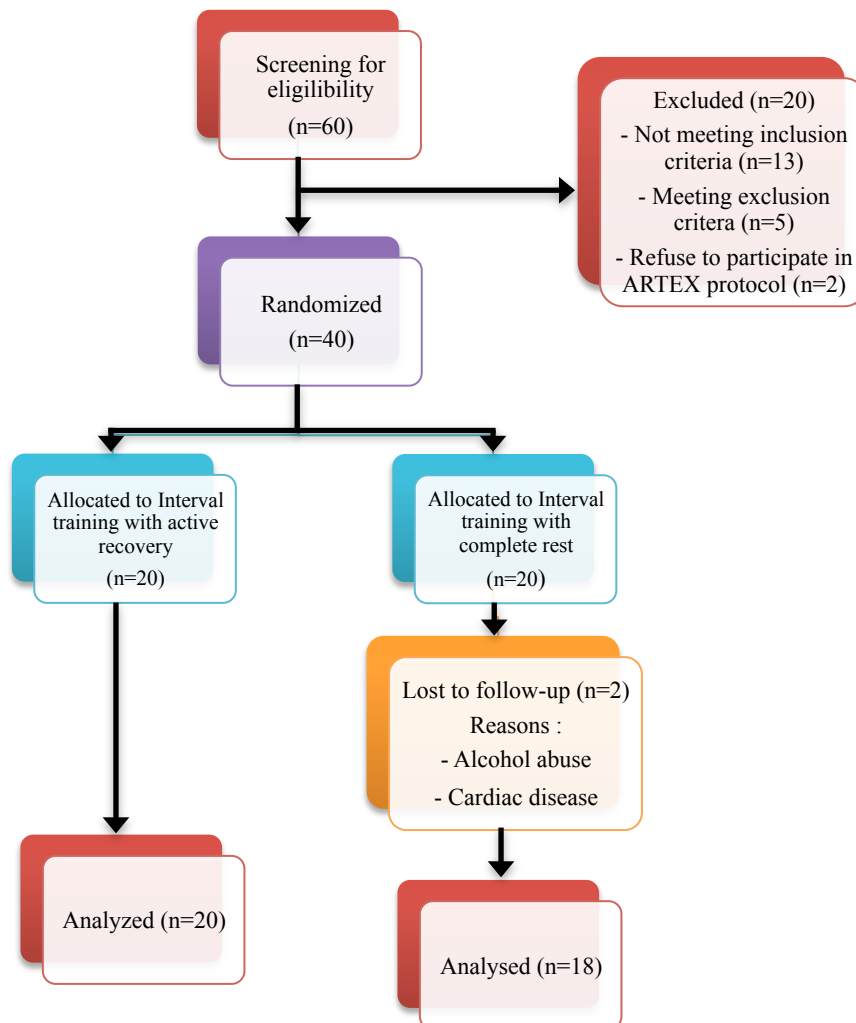


Table 1. Baseline clinical characteristics: cardiovascular risk factors of patients who participated in interval training with complete rest (ITCR) program (n=18) or in interval training with active recovery (ITAR) program (n=20). Medians ; Interquartile Range (IQR) or percentage in brackets.

Variables	groupe 1 (n=18)	groupe 2 (n=20)
Age	62 [51-64]	68 [63-70]
Male	15 (83.3%)	16 (80.0%)
Body mass index	27.2 [24.4-29.5]	29.8 [27.9-32.1]
HTA	14 (77.8%)	18 (90.0%)
Diabetes	6 (33.3%)	12 (60.0%)
If yes,		
IDD	1 (16.7%)	2 (16.7%)
NIDD	5 (83.3%)	10 (83.3%)
Dyslipidemia	15 (83.3%)	18 (90.0%)
Tobacco		
No	0	2 (10.0%)
Weaned	11 (61.1%)	15 (75.0%)
Non weaned	7 (38.9%)	3 (15.0%)
Alcohol	3 (16.7%)	3 (15.0%)
Coronary disease	6 (33,3%)	5 (25%)

IDD = insulin-dependent diabetes – NIDD = Non-insulin dependent diabetes

Diabetes was defined, according to WHO criteria: a fasting plasma glucose > 7 mmol/L or a post-prandial blood glucose > 11,1 mmol/L

Excessive alcohol consumption was defined according to the criteria of the World Health Organization (WHO): > 21 units of alcohol/week for men and > 14 units of alcohol / week for women.

Dyslipidemia was defined according to the AFSSAPS criteria (2005).

Table 2. Baseline Clinical Characteristics of the Peripheral Arterial Disease in patients who participated in ITCR program (n=18) or in ITAR program (n=20). Medians; IQR or percentage in brackets.

Variables	groupe 1 (n=18)	groupe 2 (n=20)
SBP right	132 [130-140]	140 [125-149]
ABI	0.62 [0.53-0.71]	0.78 [0.52-0.79]
Decrease in ABI after C-test (%)	58 [49-76]	54 [39-70]
PAD of two lower limbs	5 (27.8%)	11 (55.0%)
Previous surgery of lower limb arteries If yes,	6 (33.3%)	4 (20%)
Peripheral artery bypass	3 (16.7%)	2 (10%)
Arterial doppler ultrasound		
Artery stenosis	13 (72.2%)	14 (70.0%)
If yes,		
Distal	2 (15.4%)	0
Proximal	10 (76.9%)	12 (85.7%)
Both	1 (7.7%)	2 (14.3%)
Artery thrombosis	14 (77.8%)	14 (70.0%)
If yes,		
Distal	2 (14.3%)	3 (21.4%)
Proximal	11 (78.6%)	9 (64.3%)
Both	1 (7.1%)	2 (14.3%)

SPB = systolic blood pressure
SBP was measured for all patients on the right arm.

ABI = ankle-brachial index

PAD = peripheral arterial disease

Table 3. Exercise Intervention Measures in patients who participated in ITCR program (n=18) or in ITAR program (n=20). Medians ; IQR.

Variables	ITPR	ITAR	
Exercise sessions completed, (%)	100 [96-100]	100 [100-100]	P = 0,33
Session duration (min)	38.9 [38.1-39.6]	30 [30-30]	P < 0,01
Intensity, of VO2 peak (%)	52.9 [46.9-74.5]	46.8 [40.5-49.9]	P < 0,01
Intensity, of VO2 predicted (%)	34.7 [32.2-46.9]	33,3 [29.7-37.2]	P=0,46
Energy expenditure of training, (MET)	2271 [2096-3025]	1604 [1460-1787]	P < 0,01

For each patient, the session duration was determined by the average duration of all the sessions completed.

VO2 peak was evaluated during the initial test (V-test).

VO2 predicted was calculated by the Wasserman's equation on ergocycle (42). The result was multiplied by 1,1 to obtain VO2pred on a treadmill as recommended (43).

Energy expenditure of training was calculated as proposed by Gardner (41).

Figure 2. Maximal walking distance (MWD), evaluated with a graded treadmill test, before and after rehabilitation in patients completing ITCR program (n=18) and ITAR program (n= 20).

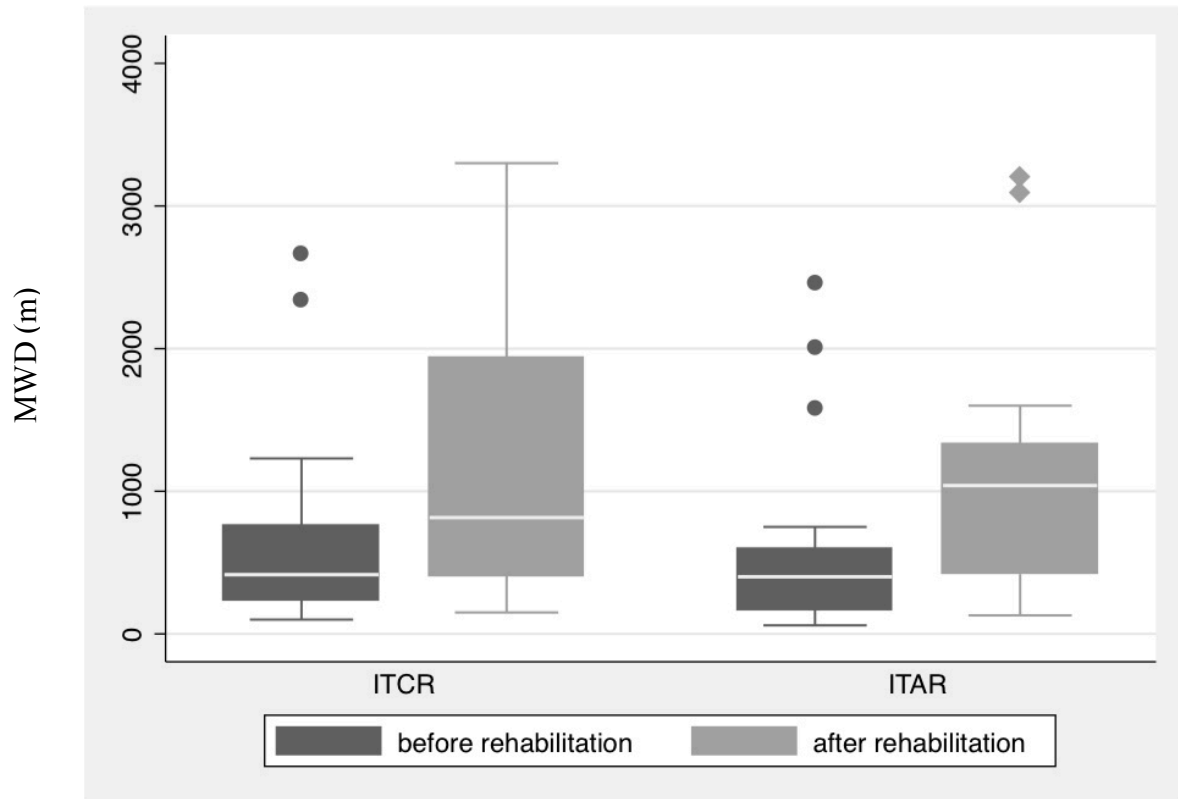


Table 4. Walking measurements evaluated with a Strandness test and a six-minute walk test, aerobic capacity and walking economy in patients who participated in ITCR program (n=18) and ITAR program (n=20). Medians ; IQR.

Variables	Pretest	Posttest	Change score
Strandness test, MWD (meters)			
ITCR	135 [100-270]	205 [140-500]	110 [20-230]
ITAR	170 [85-295]	350 [165-620]	130 [35-325]
6MWT, MWD (meters)			
ITCR	357 [245-398]	363 [330-403]	40 [-40-98]
ITAR	356 [306-403]	390[342-436]	37 [14-49]
VO2 peak (mL/kg/min)			
ITCR	18.2 [13.9-21.0]	17.7 [15.0-23.4]	1.1 [-2.2-4.6]
ITAR	17.9 [15.7-21.8]	17.8 [14.7-25.1]	0.7 [-0.5-3.0]
Percentage of VO2 predicted (%)			
ITCR	63 [54-77]	70 [52-81]	4 [-9-19]
ITAR	73 [57-90]	74 [59-100]	3 [-2-13]
VO2 at first minute (mL/kg/min)			
ITCR	8.8 [7.2-10.1]	7.7 [6.9-9.6]	-0.1 [-3.3-0.1]
ITAR	9.5 [8.2-10.6]	7.8 [6.5-9.5]	-0.74 [-3.0-0]
Transcutaneous oxygen pressure (mmHg)			
ITCR	35 [22-45]	30 [21-44]	-3 [-17-8]
ITAR	33 [22-46]	29 [19-37]	-9 [-14-6]

MWD = maximum walking distance

6MWT = six-minute walk test

To evaluate the walking economy, the VO2 was measured during the first minute of the treadmill test before and after the training (11)

Different from the ITCR group (p<0,05) : §

Figure 3. Pain evaluated with the visual analogic scale (VAS) for the first three levels of the graded treadmill test (V-test), before and after rehabilitation in patients completing ITCR program (n=18) and interval ITAR program (n= 20)

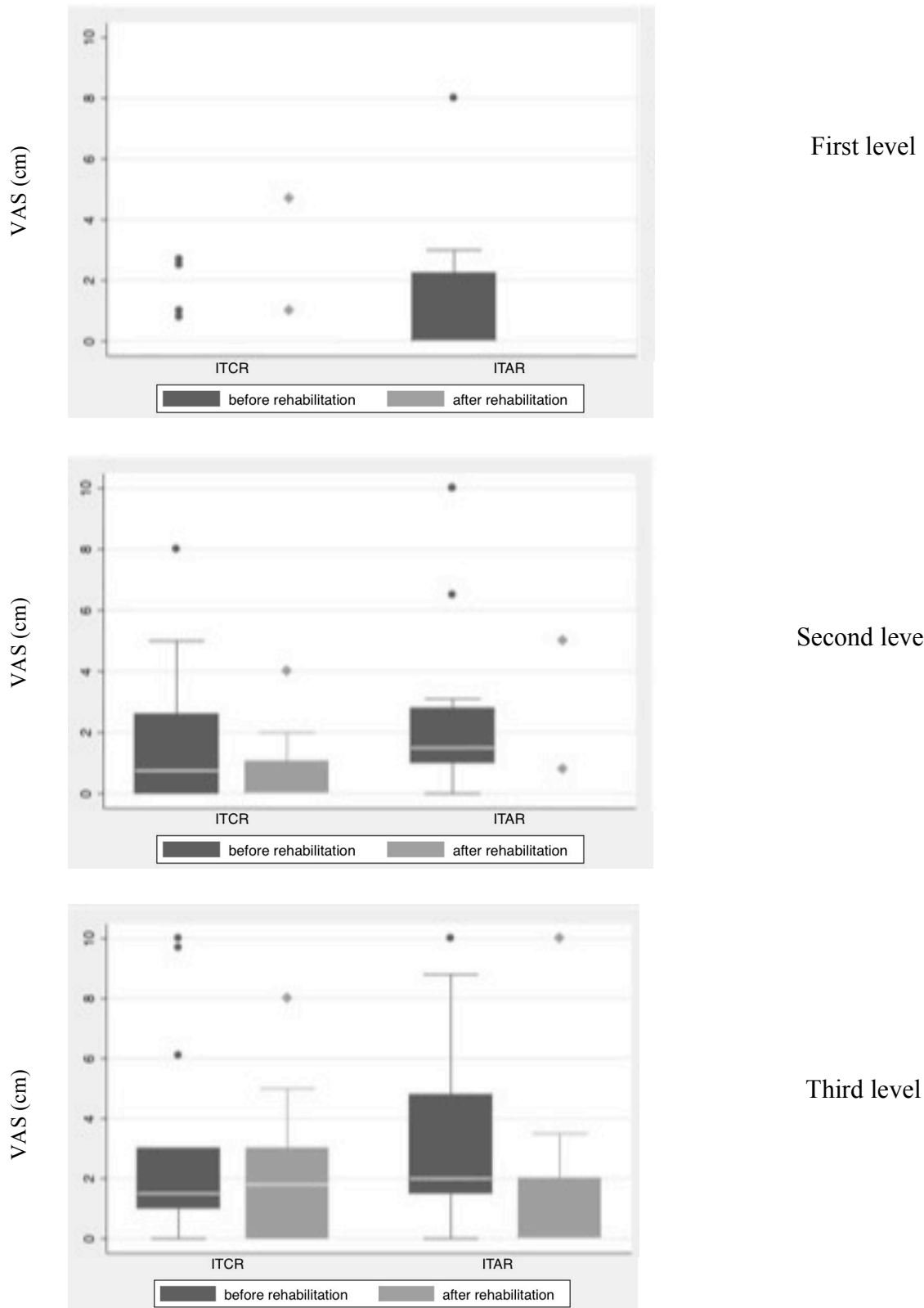


Table 5. Walking abilities evaluated with the walking impairment questionnaire (WIQ), anxiety and depression evaluated with the hospital anxiety and depression scale (HADS) before and after rehabilitation in patients completing ITCR program (n=18) and ITAR program (n= 20). Medians ; IQR.

Variables	Pretest	Posttest	Change score
WIQ walking distance score (%)			
ITCR	19 [7-54]	37 [13-66]	12 [0-19]
ITAR	33 [9-68]	60 [30-89]	20 [10-23]
WIQ walking speed score (%)			
ITCR	33 [22-50]	33 [17-43]	0 [-3-10]
ITAR	33 [25-50]	50 [33-57]	11 [3-17] §
WIQ stairs climbing score (%)			
ITCR	61 [25-88]	78 [42-88]	0 [0-25]
ITAR	54 [42-67]	67 [42-88]	5 [0-25]
HADS anxiety score			
ITCR	6.5 [4-9]	6 [4-9.5]	0 [-2-2]
ITAR	6 [4-8]	4 [4-8]	0 [-3-0]
HADS depression score			
ITCR	5 [3.5-8]	4 [3-5.5]	-1 [-3-0]
ITAR	4 [3-6]	4 [2-8]	0 [-1-1]

Different from the ITCR group (p<0,05) : §

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ANNEXE 1 - Treadmill training program for group ITCR

	Week 1	Week 2	Week 3	Week 4
First day of each week Speed	2 mph (1 mph if too difficult)	2 mph	maximum speed of W2	maximum of W3 + 0,2 mph
Slope	0%	maximum of W1	maximum of W2 + 2%	maximum of W3
Improvement of difficulty each day	slope by 0,5%	speed by 0,2 mph	slope by 2%	speed by 0,2 mph

ANNEXE 2 - Treadmill training program for group ITAR

	Week 1	Week 2	Week 3	Week 4
Work period : First session of each week Speed	70% of the maximum speed	average of W1	maximum speed of W1	maximum of W1
Slope	0%	1%	average of slopes of W2	1%
Active recovery : First session of each week Speed	40% of the maximum speed	average of W1	maximum speed of recovery of W1	maximum of W1
Slope	0%	0%	average of slopes of W1	0%
Improvement of difficulty each day Work period	speed by 0,06 mph	slope by 0,5%	speed by 0,06 mph	Slope by 0,5%
Active recovery	speed by 0,06 mph	0	speed by 0,06 mph	0

THESE SOUTENUE PAR : THOREAU Valérie

TITRE : Quatre semaines de programme quotidien d'entraînement par intervalles avec récupération active pour améliorer la marche dans la claudication artérielle: essai clinique randomisé.

CONCLUSION


Our study showed the high adherence and tolerance of a daily program (3 hours a day during four weeks) of rehabilitation dedicated to PAD patients with claudication. Interestingly, walking abilities were as much improved as with 6-month programs, 3 days a week, well described in the literature. Two treadmill trainings were assessed. As compared to the conventional interval training with complete rest when patients experienced pain, a novel program of interval training with active recovery (lower cost of energy expenditure) better improved patients' perception of walking speed, and similarly improved the maximal walking distances on a treadmill (Strandness test and graded treadmill test). The interval training with active recovery might be of interest for patients at high cardiovascular risk, due to the lower intensity of the training, and for patients available for a short period of time (one month). A follow up of this cohort of patients will investigate the possible long-term beneficial effects of these programs.

VU ET PERMIS D'IMPRIMER
Grenoble, le 28/10/2014



LE DOYEN

J.P. ROMANET



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LE PRESIDENT DE LA THESE : Pr PERENNOU

PROFESSEUR

SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté, de mes chers condisciples et devant l'effigie d'HIPPOCRATE,

Je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuitement à l'indigent et n'exigerai jamais un salaire au-dessus de mon travail. Je ne participerai à aucun partage clandestin d'honoraires.

Admis dans l'intimité des maisons, mes yeux n'y verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.

Je ne permettrai pas que des considérations de religion, de nation, de race, de parti ou de classe sociale viennent s'interposer entre mon devoir et mon patient.

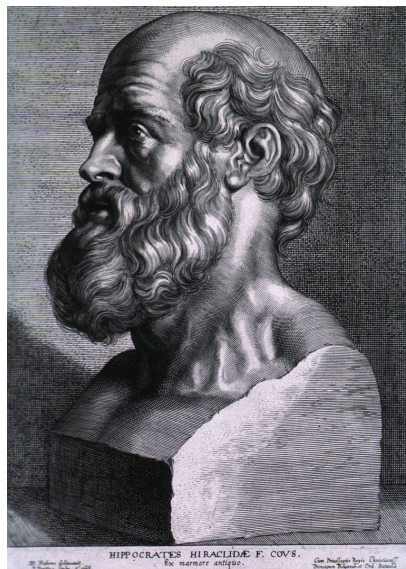
Je garderai le respect absolu de la vie humaine.

Même sous la menace, je n'admettrai pas de faire usage de mes connaissances médicales contre les lois de l'humanité.

Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses.

Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque.



**LISTE DES PROFESSEURS ET DES MAITRES DE CONFERENCE
UNIVERSITAIRES – PRATICIEN HOSPITALIER**

Faculté de médecine – Professeur des universités - Praticien Hospitalier
2013 2014

ALBALADEJO Pierre	48.01	Anesthésiologie-réanimation
ARVIEUX-BARTHELEMY Catherine	53.02	Chirurgie générale
BACONNIER Pierre	46.04	Biostat, informatique médicale et technologies de communication
BAGUET Jean-Philippe	51.02	Cardiologie
BALOSSO Jacques	47.02	Radiothérapie
BARRET Luc	46.03	Médecine légale et droit de la santé
BAUDAIN Philippe	43.02	Radiologie et imagerie médicale
BEANI Jean-Claude	50.03	Dermato-vénérologie
BENHAMOU Pierre Yves	54.04	Endocrinologie, diabète et maladies métaboliques
BERGER François	44.03	Biologie cellulaire
BETTEGA Georges	55.03	Chirurgie maxillo-faciale et stomatologie
BONAZ Bruno	52.01	Gastro-entérologie, hépatologie, addictologie
BOSSON Jean-Luc	46.04	Biostat, informatique médicale et technologies de communication
BOUGEROL Thierry	49.03	Psychiatrie d'adultes
BOUILLET Laurence	53.01	Médecine interne
BRAMBILLA CHRISTIAN	51.01	Pneumologie
BRAMBILLA Elisabeth	42,03	Anatomie et cytologie pathologiques
BRICAULT Ivan	43.02	Radiologie et imagerie médicale
BRICHON Pierre-Yves	51.03	Chirurgie thoracique et cardio-vasculaire
CAHN Jean-Yves	47.01	Hématologie

CARPENTIER Françoise	48.04	Thérapeutique, médecine d'urgence
CARPENTIER Patrick	51.04	Chirurgie vasculaire, médecine vasculaire
CESBRON Jean-Yves	47.03	Immunologie
CHABARDES Stephan	49.02	Neurochirurgie
CHABRE Olivier	54.04	Endocrinologie, diabète et maladies métaboliques
CHAFFANJON Philippe	42.01	Anatomie
CHAVANON Olivier	51.03	Chirurgie thoracique et cardio-vasculaire
CHIQUET Christophe	55.02	Ophthalmologie
CHIROSSEL Jean-Paul	42.01	Anatomie
CINQUIN Philippe	46.04	Biostat, informatique médicale et technologies de communication
COHEN Olivier	46.04	Biostat, informatique médicale et technologies de communication
COUTURIER Pascal	53.01	Gériatrie et biologie du vieillissement
CRACOWSKI Jean-Luc	48.03	Pharmacologie fondamentale, pharmacologie clinique
DE GAUDEMARIS Régis	46.02	Médecine et santé au travail
DEBILLON Thierry	54.01	Pédiatrie
DEMATTEIS Maurice	48.03	Addictologie
DEMONGEOT Jacques	(46.04)	Biostat, informatique médicale et technologies de communication
DESCOTES Jean-Luc	52.04	Urologie
ESTEVE François	43.01	Biophysique et médecine nucléaire
FAGRET Daniel	43.01	Biophysique et médecine nucléaire
FAUCHERON Jean-Luc	53.02	Chirurgie générale
FERRETTI Gilbert	43.02	Radiologie et imagerie médicale
FEUERSTEIN Claude	44.02	Physiologie
FONTAINE Eric	44.04	Nutrition

FRANCOIS Patrice	46.01	Epidémiologie, économie de la santé et prévention
GARBAN Frédéric	47.01	Hématologie, transfusion
GAUDIN Philippe	50.01	Rhumatologie
GAVAZZI Gaetan	53.01	Gériatrie et biologie du vieillissement
GAY Emmanuel	49.02	Neurochirurgie
GODFRAIND Catherine	42.03	Anatomie et cytologie pathologiques
GRIFFET Jacques	54.02	Chirurgie infantile
HALIMI Serge	44/04	Nutrition
HENNEBICQ Sylviane	54.05	Biologie et médecine du développement et de la reproduction
HOFFMANN Pascale	54.03	Gynécologie-obstétrique
HOMMEL Marc	49.01	Neurologie
JOUK Pierre-Simon	54.05	Génétique
JUVIN Robert	50.01	Rhumatologie
KAHANE Philippe	44.02	Physiologie
KRACK Paul	49.01	Neurologie
KRAINIK Alexandre	43.02	Radiologie et imagerie médicale
LABARERE José	46.01	Epidémiologie, économie de la santé et prévention
LANTUEJOUL Sylvie	42.03	Anatomie et cytologie pathologiques
LECCIA Marie-Thérèse	50.03	Dermato-vénérologie
LEROUX Dominique	47.04	Génétique
LEROY Vincent	52.01	Gastro-entérologie, hépatologie, addictologie
LETOUBLON Christian	53.02	Chirurgie générale
LEVY Patrick	44.02	Physiologie
MACHECOURT Jacques	51.02	Cardiologie
MAGNE Jean-Luc	51.04	Chirurgie vasculaire

MAITRE Anne	46.02	Médecine et santé au travail
MAURIN Max	45/01	Bactériologie-virologie
MERLOZ Philippe	50.02	Chirurgie orthopédique et traumatologie
MORAND Patrice	45.01	Bactériologie-virologie
MOREAU-GAUDRY Alexandre	46.04	Biostat, informatique médicale et technologies de communication
MORO Elena	49.01	Neurologie
MORO-SIBILOT Denis	51.01	Pneumologie
MOUSSEAU Mireille	47.02	Cancérologie
MOUTET François	50.04	Chirurgie plastique, reconstructrice & esthétique, brûlologie
PALOMBI Olivier	42.01	Anatomie
PARK Sophie	47.01	Hématologie
PASSAGIA Jean-Guy	49.02	Neurochirurgie
PAYEN DE LA GARANDERIE Jean-François	48.01	Anesthésiologie-réanimation
PELLOUX Hervé	45.02	Parasitologie et mycologie
PEPIN Jean-Louis	44.02	Physiologie
PERENNOU Dominique	49.05	Médecine physique et de réadaptation
PERNOD Gilles	51.04	Médecine vasculaire
PIOLAT Christian	54.02	Chirurgie infantile
PISON Christophe	51.01	Pneumologie
PLANTAZ Dominique	54.01	Pédiatrie
POLACK Benoît	47.01	Hématologie
POLOSAN Mircea	49.03	Psychiatrie d'adultes
PONS Jean-Claude	54.03	Gynécologie-obstétrique
RAMBEAUD Jean-Jacques	52.04	Urologie
REYT Emile	55.01	Oto-rhyno-laryngologie

RIGHINI Christian	55.01	Oto-rhyno-laryngologie
ROMANET J. Paul	55.02	Ophthalmologie
SARAGAGLIA Dominique	50.02	Chirurgie orthopédique et traumatologie
SCHMERBER Sébastien	55.01	Oto-rhyno-laryngologie
SCHWEBEL Carole	48.02	Réanimation, médecine d'urgence
SCOLAN Virginie	46.03	Médecine légale et droit de la santé
SERGENT Fabrice	54.03	Gynécologie-obstétrique
SESSA Carmine	51.04	Chirurgie vasculaire
STAHL Jean-Paul	45.03	Maladies infectieuses, maladies tropicales
STANKE Françoise	48.03	Pharmacologie fondamentale
TAMISIER Renaud	44.02	Physiologie
TIMSIT Jean-François	48.02	Réanimation
TONETTI Jérôme	50.02	Chirurgie orthopédique et traumatologie
TOUSSAINT Bertrand	44.01	Biochimie et biologie moléculaire
VANZETTO Gérald	51.02	Cardiologie
VUILLEZ Jean-Philippe	43.01	Biophysique et médecine nucléaire
WEIL Georges	46.01	Epidémiologie, économie de la santé et prévention
ZAOUI Philippe	52.03	Néphrologie
ZARSKI Jean-Pierre	52.01	Gastro-entérologie, hépatologie, addictologie

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APTTEL Florent	55.02	Ophtalmologie
BOISSET Sandrine	45.01	Bactériologie, virologie
BONNETERRE Vincent	46.02	Médecine et santé au travail
BOTTARI Serge	44.03	Biologie cellulaire
BOUZAT Pierre	48.01	Anesthésiologie-réanimation
BRENIER-PINCHART M.Pierre	45.02	Parasitologie et mycologie
BRIOT Raphaël	48.04	Thérapeutique, médecine d'urgence
CALLANAN-WILSON Mary	47.01	Hématologie, transfusion
DECAENS Thomas		
DERANSART Colin	44.02	Physiologie
DETANTE Olivier	49.01	Neurologie
DIETERICH Klaus	47.04	Génétique
DUMESTRE-PERARD Chantal	47.03	Immunologie
EYSSERIC Hélène	46.03	Médecine légale et droit de la santé
FAURE Julien	44.01	Biochimie et biologie moléculaire
GILLOIS Pierre	46.04	Biostat, informatique médicale et technologies de communication
GRAND Sylvie	43.02	Radiologie et imagerie médicale
GUZUN Rita	44.04	Nutrition
LAPORTE François	44.01	Biochimie et biologie moléculaire
LARRAT Sylvie	45.01	Bactériologie, virologie
LAUNOIS-ROLLINAT Sandrine	44.02	Physiologie
LONG Jean-Alexandre	52.04	Urologie
MAIGNAN Maxime	48.04	Médecine d'urgence
MALLARET Marie-Reine	46.01	Epidémiologie, économie de la santé et prévention
MARLU Raphaël	47.01	Hématologie

MAUBON Danièle	45.02	Parasitologie et mycologie
MC LEER (FLORIN) Anne	42.02	Cytologie et histologie
MOUCHET Patrick	44.02	Physiologie
PACLET Marie-Hélène	44.01	Biochimie et biologie moléculaire
PAYSANT François	46.03	Médecine légale et droit de la santé
PELLETIER Laurent	44.03	Biologie cellulaire
RAY Pierre	47.04	Génétique
RIALLE Vincent	46.04	Biostat, informatique médicale et technologies de communication
ROUSTIT Matthieu	48.03	Pharmacologie clinique
ROUX-BUISSON Nathalie	44.01	Biochimie et génétique moléculaire
SATRE Véronique	47.04	Génétique
SEIGNEURIN Arnaud	46.01	Epidémiologie, économie de la santé et prévention
STASIA Marie-Josée	44.01	Biochimie et biologie moléculaire