

RESEARCH ARTICLE

Intra Arterial Heparin Flushing Increases Cerebral Blood Flow in Chronic Ischemic Stroke PatientsTerawan Agus Putranto^{1,2,*}, Irawan Yusuf^{1,2}, Bachtiar Murtala¹, Andi Wijaya^{3,4}¹Postgraduate Program in Medical Science, Faculty of Medicine, Hasanuddin University, Jl. Perintis Kemerdekaan Km.10, Makassar, Indonesia²Gatot Soebroto, Indonesia Army Central Hospital, Jl. Abdul Rahman Saleh No.24, Jakarta, Indonesia³Postgraduate Program in Clinical Biochemistry, Faculty of Medicine, Hasanuddin University, Jl. Perintis Kemerdekaan Km.10, Makassar, Indonesia⁴Prodia Clinical Laboratory, Jl. Cisangkuy No.2, Bandung, Indonesia

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Received date: Apr 13, 2016; Revised date: May 31, 2016; Accepted date: Jun 2, 2016

Abstract

BACKGROUND: Recently, stroke therapy is focused on reperfusion therapies for restoring cerebral blood flow (CBF) and minimizing the undesired effects of neuron ischemia. However, the thrombolytic therapy to restore CBF was restricted with narrow time window. On the other hands, not many patients can reach the treatment immediately after the onset of stroke. A wider time window therapy that might increase CBF would probably helpful. This study aims to investigate the CBF improvement after intra arterial heparin flushing (IAHF) therapy in chronic stroke patients.

METHODS: A clinical trial was conducted with time sampling. We collected chronic ischemic stroke subjects (with stroke onset ≥ 30 days) within periods February-September 2015. We investigated CBF before and after IAHF treatment in 75 chronic stroke patients. The difference

before and after IAHF treatment in subgroup which is classified with infarct size and lesion area was tested. CBF was measured using MRI Quality Arterial Spin Labeling (qASL) with region of interest around infarct lesion.

RESULTS: We found a significant CBF improvement ($p < 0.001$) around infarct area after IAHF treatment with average 10.39mL/100g/min raised. CBF improvement was found in lacunar infarct ($p < 0.001$) and non lacunar ($p < 0.001$), also in infarct in cortical ($p < 0.05$), subcortical ($p < 0.001$) and both area ($p < 0.05$).

CONCLUSION: IAHF is associated with increased CBF around infarct area and IAHF probably offers some benefit for chronic stroke.

KEYWORDS: IAHF, CBF, chronic stroke, ischemic, lacunar, non lacunar, cortical lesion, subcortical lesion

*Indones Biomed J. 2016; 8(2): 119-26***Introduction**

Stroke is the second leading cause of adult mortality and long term disability. Globally, stroke is also known as production and economic burdens.(1,2) This has been provoking a lot of studies to find out a better understanding on stroke therapy in the last decades.(3,4)

Multiple clinical trials showed sudden decrease of cerebral blood flow (CBF) that can lead to a complex pathophysiology of ischemic cascade including

excitotoxicity, inflammation, oxidative damage and ion imbalance, which lead to cerebral infarct CBF restoration either spontaneously or by reperfusion therapy, is needed in time to recover glial and neuron cells after ischemic injury. Recent studies are still focusing on how to improve CBF effectively.(5) The penumbra was classically defined as the hypoperfused tissue surrounding the ischemic core in which blood flow is too low to maintain electric activity but sufficient to preserve ion channels. New definition of penumbra defines that penumbra is peri-infarcted tissue which serves as boundary zone between dead and healthy

tissue. From a therapeutic point of view, the ischemic penumbra is a target for brain plasticity and neurorepair treatments.(6)

Thrombosis plays an important role in ischemic stroke pathogenesis. Many attempts had been done to find the most suitable thrombolytic therapy regiment to obtain higher cerebral perfusion after ischemia.(7,8, 9) So far only serine protease tissue-type plasminogen activator was approved by FDA as a thrombolytic agent for stroke treatment. Randomized controlled trials (RCT) data from European Cooperative Acute Stroke Study (ECASS) III and the Safe Implementation of Thrombolysis in Stroke International Stroke Treatment Registry (SITS-ISTR) showed that intravenous recombinant tissue plasminogen activator can effectively improve the outcome of patients with ischemic stroke when delivered within 3-4.5 hours after stroke onset.(8,10) However, many patients with viable penumbra were not treated by reperfusion therapies.(6) In Gatot Soebroto Army Central Hospital, 57.33% of stroke patients came in chronic phase (after 30 days). Thus, new therapeutic strategies with a wider window time will be very useful to reduce after ischemic morbidity in chronic phase.(10)

After recanalization treatment with recombinant tissue plasminogen activator, clot dissolution followed by a significant hyperemia within the ischemic region immediately occurs. However, this is followed by a post ischemic hypoperfusion, which can last for hours. This is described as the 'no-reflow phenomenon' and has been attributed to the narrowing of capillaries.(11) Capillary pericytes has an important role in the long-lasting blood flow decrease following ischemia. Pericytes constrict capillaries at the start of a stroke, and then stay in rigor (because no ATP is available to relax their contractile filaments), causing the capillaries to remain small for the passage of red blood cells. Suppression of oxidative and nitrosative stress prevents these pericytes constriction, restores the patency of capillaries, and improves tissue recovery.(12) This showed that the current treatment have limitation in window time and in inducing microvascular reperfusion.

Digital subtraction angiography (DSA) which was modified with intra arterial heparin flushing (IAHF) in Gatot Soebroto Army Central Hospital showed a clinical improvement in chronic stroke patients empirically. In radio intervention procedure, heparin usually used as flushing solution for catheterization.(13) Heparin not only plays role as an anticoagulant but also plays role as a fibrinolytic. Heparin increases plasminogen conversion into plasmin by stimulating tissue plasminogen activator.(14) Heparin has potential in increasing thrombolysis by inhibiting thrombin

activatable fibrinolysis inhibitor (TAFI) formation.(15) Thus, heparin is commonly used to treat both arterial and venous thrombosis because of its safety-proven reason.(3,16,17) Intravascular studies showed that heparin therapy can reduce the clot size (18), suggested by its potency in brain reperfusion after ischemic. The potential of heparin as antioxidant is well known, so that it is used in hemodialysis to suppress oxidative stress during dialysis.(19)

Methods

Sample and Population

This study was approved by Hasanuddin University Ethical Committee with register number UH14110582 and was involving 75 chronic ischemic stroke patients (with stroke onset ≥ 30 days) in Cerebrovascular Center Gatot Soebroto Indonesian Army Central Hospital, started from February 2015 until September 2015. Subjects participated voluntarily and signed the informed consent. Subjects were assessed for their age, sex, stroke onset, hemiparesis side, lesion area, infarct size (lacunar if lesion < 15 mm or non lacunar if ≥ 15 mm) and stroke risk factors, including dyslipidemia (total cholesterol > 200 mg/dL, triglycerides > 160 mg/dL, LDL > 100 mg/dL and/or HDL < 35 mg/dL), hypertension (blood pressure $> 140/90$ mmHg), diabetes mellitus (fasting blood glucose > 126 mg/dL or post prandial glucose > 200 mg/dl or below with glucose lowering agents), hyperuricemia (uric acid > 7 mg/dL), hypercoagulation (prothrombin time > 11.8 seconds, APTT > 47 seconds, fibrinogen > 350 mg/ dL and D-dimer > 400 ng/mL). Heart disease assessed by cardiologist after clinical examination and electrocardiography examination.

CBF Measurement

CBF was measured before and 4 hours after the IAHF therapy using sequence of MRI ASL Special work packages ASP "Addin Special Sequence Package": N4_818_VD13A_PFEUJODJ_Adv3DASL with single time inversion and protocol as below: field of view (FOV) 256x256 mm; slice thickness 5 mm; matrix size 64x64 pixel; repetition time (TR) 4000 ms; time to echo (TE) 18 ms; bandwidth 2.365 Hz/pixel; coil head matrix; flip angle 180 degree; bolus duration 700 ms; time inversion 1990 ms; window width 200; window center 100. CBF map is produced with Buxton parameter model. Region of interest was drawn around lesion using Syngovia post processing packages. CBF measurement unit is mL/100 g/min.

IAHF-modified DSA Procedure

Initially, 5000 IU heparin was diluted with 500 mL Normal Saline Otsu (Otsuka, Lawang, Indonesia). Topical eutectic mixture of local anesthetics (EMLA) was applied on femoral artery area, continued with povidone iodine 7.5% and alcohol 70%. Local anesthetic, a lidocain, was injected intra cutaneously and subcutaneously. Femoral artery was punctured with abocath 18 G, and short guide wire was inserted. Fluoroscopy was performed to see the anatomical imaging. Diluted heparin was flushed intra arterial in both right and left carotid arteries and vertebral arteries. After completing the flushing process, femoral artery bleeding was stopped using either conventional technique with pressure given to puncture site using sandbag for 8 hours or angio seal.

Statistical Analysis

Statistical analysis was performed with SPSS 15.0. Kolmogorov-Smirnoff test was performed to find the data distribution model. The differences before and after IAHF treatment were tested using paired T-test or Wilcoxon test alternatively with *p* value of 0.05 were considered significant. The difference before and after IAHF treatment in subgroup classified with age, sex, stroke onset, infarct size, and lesion area were also tested using paired T-test or Wilcoxon test alternatively with *p* value of 0.05 were considered significant.

Results

Seventy five chronic ischemic stroke patients participated in our study. Subjects' characteristics can be found in Table 1. CBF value was obtained with magnetic resonance imaging (MRI) quality arterial spin labeling (qASL) after post processing (Figure 1). Region of interest was placed among infarct lesion in three slices on every patient and the value was recorded. The average of pre-treatment CBF value was 25.22±13.09 mL/100g/min 35.61±18.63 mL/100g/min after IAHF treatment. The difference between post and pre-treatment was 10.39 mL/100g/min or 41.20% improvement. Wilcoxon test was performed to analyze the differences. A significant differences CBF value was found before and after IAHF treatment (*p*<0.001) (Table 2).

After the subgroup was classified based on age, sex, stroke onset, infarct size and lesion area, we analyze it statistically. Wilcoxon alternative test showed significant difference between pre- and post-test CBF in both male

(24.18±11.98 mL/100g/min and 33.83±17.25 mL/100g/min; *p*<0.001) and female subjects (28.77±16.28 mL/100g/min and 41.68±22.24 mL/100g/min; *p*<0.001). In grouping based on age, significant difference was shown in subgroup subjects with age 41-60 years old (22.81±11.07 mL/100g/min and 31.73±14.68 mL/100g/min; *p*<0.001) and subgroup >60 years old (30.27±15.94 mL/100g/min and 43.12±20.75 mL/100g/min; *p*<0.001). But there was not found significant difference in subgroup subjects with age 18-40 years old (33.58±17.32 mL/100g/min and 52.74±43.15 mL/100g/min; *p*>0.05) (Table 3).

Significant difference was also found in all subgroup of stroke onset, subgroup with onset <1 year (29.26±13.82

Table 1. Subjects characteristic.

Variables	Number of subjects (percentage)
Sex	
Male	58 (77.33%)
Female	17 (22.67%)
Age	
<40 years old	3 (4%)
41-60 years old	52 (69.33%)
>60 years old	20 (26.67%)
Onset	
<1 year	44 (58.67%)
1-3 years	26 (34.67%)
>3 years	5 (6.67%)
Hemiparesis	
Right	38 (50.67%)
Left	37 (49.33%)
Lesion size	
Lacunar	48 (64%)
Non Lacunar	27 (36%)
Lesion Area	
Cortex	11 (14.67%)
Subcortex	57 (76%)
Cortex-Subcortex	7 (9.34%)
Risk Factor	
Dislipidemia	60 (80%)
Hypertension	52 (69.33%)
Diabetes Mellitus	24 (32%)
Hyperuricemia	17(22.67%)
Hypercoagulation	12 (16%)
Heart Disease	16 (21.33%)

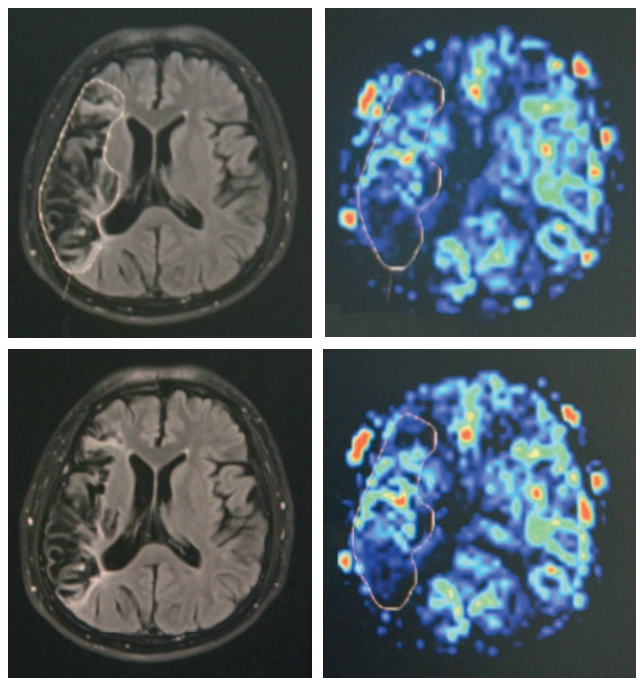


Figure 1. Post processing qASL using Syngovia. CBF pre-treatment in region of interest (upper right) (divided with 10) 23.45 mL/100g/min compared with post treatment (lower right) 34.01 mL/100g/min in the same region using autoalignment.

mL/100g/min and 41.13 ± 18.13 mL/100g/min; $p < 0.001$), 1-3 years (17.83 ± 8.89 mL/100g/min and 25.77 ± 16.44 mL/100g/min; $p < 0.001$) and > 3 years (28.17 ± 9.13 mL/100g/min and 38.20 ± 15.05 mL/100g/min; $p < 0.05$) (Table 3).

Wilcoxon alternative test showed significant difference between pre- and post-test CBF in subjects with stroke ischemic in cortical lesion (22.29 ± 12.71 mL/100g/min and 32.83 ± 16.83 mL/100g/min; $p < 0.05$), subcortical lesion (26.60 ± 13.47 mL/100g/min and 37.34 ± 19.38 mL/100g/min; $p < 0.001$) and both cortical-subcortical lesion (18.62 ± 8.28 mL/100g/min and 25.93 ± 12.35 mL/100g/min; $p < 0.05$) (Table 3). CBF average increased as much as 10.54 ± 8.61 mL/100g/min in cortical lesion, 10.74 ± 10.48 mL/100g/min in subcortical lesion and 7.31 ± 6.511 mL/100g/min in cortical-subcortical lesion (Figure 2).

Wilcoxon alternative test showed significant difference between pre- and post-test CBF in subjects with stroke ischemic in lacunar infarct (28.26 ± 13.72 mL/100g/min and 39.83 ± 19.87 mL/100g/min; $p < 0.001$) and non lacunar infarct (19.81 ± 10.01 mL/100g/min and 28.09 ± 13.50 mL/100g/min; $p < 0.001$) (Table 3). CBF average increased as much as 11.57 ± 11.06 mL/100g/min in lacunar infarction and 8.28 ± 7.05 mL/100g/min in non lacunar or wide infarction (Figure 3).

Discussion

Heparin was used for thrombosis treatment for a long time. DSA followed by IAHF treatment performed in chronic ischemic stroke patients in our study showed a significant improvement in CBF value, about 10.39 mL/100g/min around the infarct area ($p < 0.001$) in IAHF treated group. Rather than restoring the CBF into normal value, this improvement happened due to partial restoring of microcirculation. In this study, the CBF value increased after 4 hours of IAHF treatment. CBF changes (Δ CBF) can also reflecting vasodilatation or metabolic changes (20) and not always reflecting increase of micro vessel density so that was not have a high sensitivity as a angiogenesis marker (21). Increasing CBF here was not associated with angiogenesis because process sufficient time is needed to form angiogenesis. Slevin described that the new blood vessels formation were initiated through vascular buds, forming a connection with intact micro vessels after weeks post-ischemia.(22)

Therapy strategy to reduce microvascular obstruction can increase oxygen flow to the tissue where entrapping red blood cells could not be circulated in capillaries. Serum reflow can increase cell survival after ischemia. Recent studies showed that CBF improvement support glial and neuronal cells recovery and related to neuronal activities but limited to ischemic cells without irreversible damage as known as penumbra.(5,23) Functional reorganization supported by survived cells around infarct core or penumbra is an important mechanism in motor recovery after stroke.(24)

CBF improved in all stroke onset subgroup, even in subjects with stroke onset more than 3 years. In subject with stroke onset started 6 years ago, less Δ CBF were obtained compare to other subjects. This showed that although IAHF could improve CBF in all chronic stroke subjects in this study, the sooner IAHF performed is the better. CBF improved in both female and male subjects suggested that sex give no differences in CBF improvement. In 3 subjects in the subgroup age 18-40 years old, CBF improvement was high (19.16 ± 26.03 mL/100g/min) but not statistically significant ($p > 0.05$). We found increasing CBF in both lacunar and non lacunar infarct, with the higher increasing CBF is in subjects with lacunar stroke. We also found CBF increasing in patients with cortical, subcortical and both cortical-subcortical lesion. Lower increasing CBF was

Table 2. CBF differences before and after IAHF treatment.

CBF value (mL/100g/min)	Mean±SD	Median	Mean	p
Pre-treatment	25.22±13.09	23.81	5.79-78.29	<0.001
Post-treatment	35.61±18.63	32.66	6.33-109.72	

Table 3. Correlation analysis between spirometric paramaters and the risk factors.

CBF Value	Pre-Test		Post-Test		ΔCBF	p
	Mean±SD	Median (Min-Max)	Mean±SD	Median (Min-Max)		
Sex						
Male	24.18±11.98	24.01 (5.79-55.04)	33.83±17.25	32.50 (6.33-102.30)	9.65±9.79	<0.001
Female	28.77±16.28	23.36 (8.78-78.29)	41.68±22.24	36.43 (9.67-109.72)	12.91±10.06	<0.001
Age						
18-40 years old	33.58±17.32	27.64 (20.01-53.09)	52.74±43.15	32.37 (23.55-102.30)	19.16±26.03	0.109
41-60 years old	22.81±11.07	22.15 (6.24-55.04)	31.73±14.68	30.84 (9.32-80.05)	8.92±7.94	<0.001
>60 years old	30.27±15.94	26.62 (5.79-78.29)	43.12±20.75	43.22 (6.33-109.72)	12.89±10.74	<0.001
Stroke Onset						
<1 year	29.26±13.82	25.69 (7.04-78.29)	41.13±18.13	38.06 (15.89-109.72)	11.87±9.88	<0.001
1-3 years	17.83±8.89	15.73 (5.79-37.73)	25.77±16.44	23.93 (6.33-80.05)	7.94±10.21	<0.001
>3 years	28.17±9.13	27.64 (18.63-42.42)	38.20±15.05	32.98 (21.60-61.69)	10.03±6.51	0.043
Lesion Area						
Cortex	22.29±12.71	18.37 (6.24-47.86)	32.83±16.83	27.04 (9.83-59.57)	10.54±8.61	0.003
Subcortex	26.60±13.47	25.32 (5.79-78.29)	37.34±19.38	33.82 (6.33-109.72)	10.74±10.48	<0.001
Cortex-Subcortex	18.62±8.28	21.65 (7.36-29.77)	25.93±12.35	32.49 (0.92-41.58)	7.31±6.51	0.018
Infarct Size						
Lacunar	28.26±13.72	26.01 (7.04-78.29)	39.83±19.87	34.79 (9.67-109.72)	11.57±11.06	<0.001
Non-lacunar	19.81±10.01	19.75 (5.79-47.94)	28.09±13.50	27.04 (6.33-53.60)	8.28±7.05	<0.001

obtained if infarct area was wide or involved both cortical subcortical areas so that involving more blood vessel obstruction and wider core infarct lesion with irreversible damage. Our finding showed that IAHF has the potential to restore both macro and microcirculation by clot lytic

and facilitate vasodilatation supported with its ability as anantioxidant.

Heparin, an anticoagulant containing a number of additional effects such as anti-inflammatory and antioxidant, is a fundamental substance used during hemodialysis

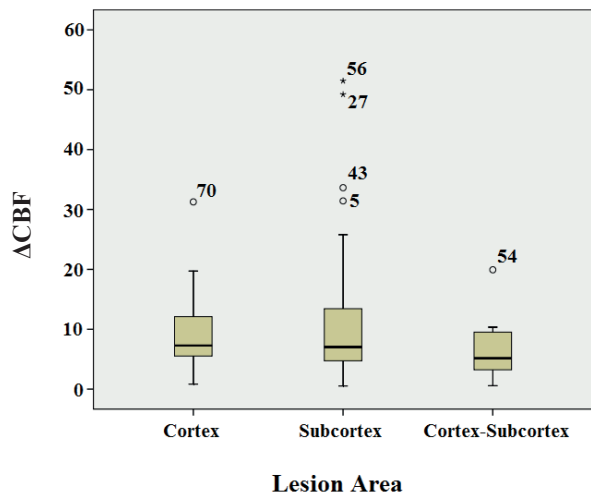


Figure 2. CBF changes in lesion area subgroup. Subjects with lesion in subcortex has the highest changes with average 10.74±10.48 mL/100g/min, followed by cortex (10.54±8.61 mL/100g/min), and cortex-subcortex (7.31±6.51 mL/100g/min).

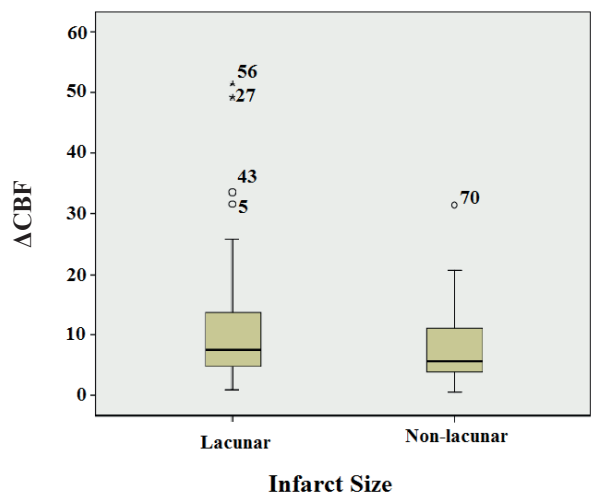


Figure 3. CBF changes in infarct size subgroup. Patients with lacunar infarct has higher changes with average 11.57±11.06 ml/100gr/min, followed by non lacunar infarct 8.28±7.05 ml/100gr/min.

sessions.(19) Heparin is glycosaminoglycan compound with highest negative charge density compare to any other molecules. Heparin affects free radical activity by modulating environment around the free radical. Heparin inhibits iron that catalyzing free radical peroxidation from linoleic acid. Heparin inhibits diene and thiobarbituric acid conjugation from reaction involving linoleic acid and iron. Heparin boosts the antioxidant effect of superoxidedismutase by releasing it near the endothelial cells of the vessels. On the

other hand, heparin, as a sink of free radicals of oxygen in addition to iron and copper, the well known oxidants in inflamed tissues, plays properly its antioxidant role.(25) After ischemic, tissue level of acidity is lower than normal due to lactate accumulation. This variation alters antioxidant activity but heparin is known to have good activity even in low acidity environment.(19,26).

Heparin with anti-inflammatory and antioxidant properties is capable to suppress oxidative stress.(19) Thus antioxidant properties prevent pericytes constriction, restore capillary patency and increase tissue recovery.(12)

Study by Nawashiro, *et al.*, in effort to achieve CBF improvement performed by transcranial light-emitting diode (LED) in acute stroke patients, showed 20% increase in CBF leads to patients outcome improvement, tested by hand movement to reach things close to them. However, this therapy needs 73 days long with 146 treatments series to reach the desirable effect.(27) Earlier studies showed that vasodilator agents (acetazolamide, nylidrine, xylandelate, hydergine, papaverine) significantly increase CBF in acutestroke patients.(28) Statin is also used in some studies as an alternative drug to increase CBF. Mechanical recanalization with endovascular stent on vascular stenosis showed CBF increases as much as 21%±10%.(29)

Sustainable physical therapies are still becoming a major strategy to obtain CBF improvement in chronic stroke patients. Study by Perrey, *et al.*, using transcranial Doppler (TCD) reported that aerobic exercise supports increase in CBF increasing both global and regional.(20) They attributed task-induced vasodilatation to an increased demand for cerebral metabolism in response to neuronal activity, and found that during physical activities, CBF increases to supply adequate oxygen into the brain, and the CBF regulation seems to be crucial for the maintenance of cardiovascular homeostasis.(20,30)

IAHF potency for vessel recanalization was not observed in this study. Substantial experimental data and recent clinical evidences suggested that tissue reperfusion is a better predictor for after-thrombolysis outcome compare to recanalization. IAHF treatment in this studies showed a significant increased of CBF (41.20%), higher than any other CBF increasing strategies. Dalkara reported that therapeutic approaches aiming to reduce microvascular obstructions may improve the success rate of recanalization therapies. Substantially, by promoting oxygen delivery to the tissue, where entrapped erythrocytes cannot circulate in capillaries, marching with serum flow may improve survival of the under perfused tissue. These heaps upon the exciting

possibility about reperfusion therapy benefit for restoring microcirculatory function dependent from any onset, due to penumbra survival based on adequate blood supply.(23)

Conclusion

We found that IAHF treatment can significantly improve CBF value in chronic ischemic stroke patients. This study gives a new hope that reperfusion therapy with IAHF can give benefit to increase microcirculatory function to support penumbral recovery with a wider window therapy.

Acknowledgements

We would like to thank Gatot Soebroto Indonesia Army Central Hospital, Hasanuddin University and The Prodia Education and Research Institute for their invaluable supports to this study.

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