

Content available at: <https://www.ipinnovative.com/open-access-journals>

IP Indian Journal of Neurosciences

Journal homepage: <https://www.ijonline.org/>

## Original Research Article

## No-Reflow phenomenon in the perspective of endovascular neurosurgery

Kuldeep Yadav<sup>1,\*</sup>, Deepak Kumar Singh<sup>1</sup>, Mohd. Kaif<sup>1</sup>, Diwakar Shankar<sup>1</sup><sup>1</sup>Dept. of Neurosurgery, Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, Uttar Pradesh, India

## ARTICLE INFO

## Article history:

Received 13-04-2021

Accepted 16-05-2021

Available online 25-09-2021

## Keywords:

No reflow

Angiography

Brain Angiography

Neuroendovascular

## ABSTRACT

**Introduction:** Concept of No-Reflow (NR) phenomenon is largely studied in cardiological intervention characterised by the failure of myocardial reperfusion despite the absence of mechanical obstruction of large and medium sized vessels. NR negatively affects outcome of procedure, so there is great importance of prediction and management. The objective was to introduce concept of NR in neuro-intervention and have an idea of incidence and independent predictors of NR in patients with post intervention no-reflow in large and medium sized brain arteries.

**Materials and Methods:** This was a single-centre prospective case– control study between march 2017-march 2021 in the department of Neurosurgery, Dr. R.M.L.I.M.S., Lucknow, India. Cases were subjects who suffered NR, and the control comparators were those who did not. Clinical outcomes were documented. Salient variables relating to the patients and their presentation, history and angiographical findings were documented.

**Results:** Of 153 consecutive patients, 11(7.2%) suffered from NR, with all cases occurring post intervention in the form of coiling with or without stent/balloon support or flow diverter placement with or without coiling. Patients with NR had increased risk of in-hospital death and disability (1 patient/9.1% death, 8 patients/72.72% with one or multiple neurological dysfunction with varying severity) in comparison to patients without NR (4 patients/2.8% deaths and 12 patients/8.5% disabilities, out of 142 patients). From baseline variables available prior to neuro-endovascular surgery, the independent predictors of NR were increased complexity of pathology, admission systolic hypertension, weight of more than 75 kg and history of hypertension, history of DM, history of ischaemic vascular disease/dissection/aneurysm in the brain or elsewhere, history of systemic arteritis, history of autoimmune disease and atherosclerosis, history of smoking, female gender, elderly.

**Conclusion:** Patients with NR have a higher rate of morbidity and mortality following ischaemia and embolism. Predictors of NR include lesion complexity, systolic hypertension and high body weight, female gender, elderly, dyslipidaemia and preexisting arterial disease. Further validation of this risk model is required with larger number of patients and multicenter studies.

This is an Open Access (OA) journal, and articles are distributed under the terms of the [Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License](https://creativecommons.org/licenses/by-nc-sa/4.0/), which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: [reprint@ipinnovative.com](mailto:reprint@ipinnovative.com)

## 1. Introduction

The pathophysiology of NR is complex and is not fully understood.<sup>1–3</sup> It involves much more than just distal embolization of thrombotic debris. Indeed, many phenomena contribute to NR: leukocyte infiltration,

vasoconstriction, activation of inflammatory pathways and cellular edema.<sup>4,5</sup> Recently, experimental data demonstrated the important roles played by vascular damage and haemorrhage in the establishment of NR. Vascular permeability at the endothelial level appears to be a major factor in NR.<sup>6,7</sup> It starts with endothelial injury by endovascular hardware.

\* Corresponding author.

E-mail address: [ykd230@gmail.com](mailto:ykd230@gmail.com) (K. Yadav).

A major regulator of endothelial integrity is vascular endothelial growth factor (VEGF), which was originally called vascular permeability factor. VEGF is expressed in response to endothelial injury. In a resting state, VEGF receptor 2 forms a complex with vascular endothelial (VE)-cadherin,<sup>8,9</sup> an endothelial-specific adhesion protein that stabilizes intercellular adherence junctions. Injury-induced VEGF, when binding to VEGF receptor 2, dissociates the VEGF receptor 2/VE-cadherin complex, leading to an increase in endothelial permeability. VEGF activates Src phosphorylation, which then induces tyrosine phosphorylation of VE-cadherin and its internalization; this reduces the amount of VE-cadherin available at interendothelial junctions, thus leading to disruption of endothelial barrier integrity. In vivo, VE-cadherin phosphorylation is also modulated by the haemodynamic forces and shear stress to which endothelial cells are exposed. So, driven by its phosphorylation state, VE-cadherin plays a major role in maintaining strong interendothelial junctions. In experimental models, vascular permeability plays a central role in NR. However there are few data from human patients on the basal phosphorylation levels of VE-cadherin, which might represent a new angle for preventing or treating NR. Endothelial hypersensitivity is another factor.

One other factor is ruptured plaque with thrombus and atherosclerotic material leading to distal embolization of microthrombi and plaque components. This distal embolization is also involved in the NR phenomenon.<sup>10</sup>

The term NR came naturally after the observation of the absence of flow despite correct stents and/or coils placement or sometime only after angiography and catheter manipulation.

NR can be quantified in angiography by TICI classification (TICI 1-no/minimal reperfusion, 2a-partial filling less than 50% territory, 2b-partial filling more than 50% territory, TICI 2c-near complete perfusion except slow flow or few distal cortical emboli, tici 3-complete perfusion)

## 2. Materials and Methods

This was an open single center prospective case– control study. Neurosurgery department of Dr. R.M.L.I.M.S. have biplane cath lab of Toshiba. Here we provide all kind of endovascular neurosurgery facility. From march 2017 to march 2021, we prospectively analysed 153 patients who underwent major neuro-endovascular procedures. 81 patients were female and 72 patients were male. 142 patients presented with subarachnoid haemorrhage of varying grade after ruptured intracranial aneurysm. In these 142 patients recieved coiling with or without stent/flow diverter was done. Rest 11 patients presented with unruptured giant intracranial aneurysm. In these unruptured giant aneurysm, flow diverter/intrasaccular device was placed. The overall outcome of the patients was dependent upon pre-procedural

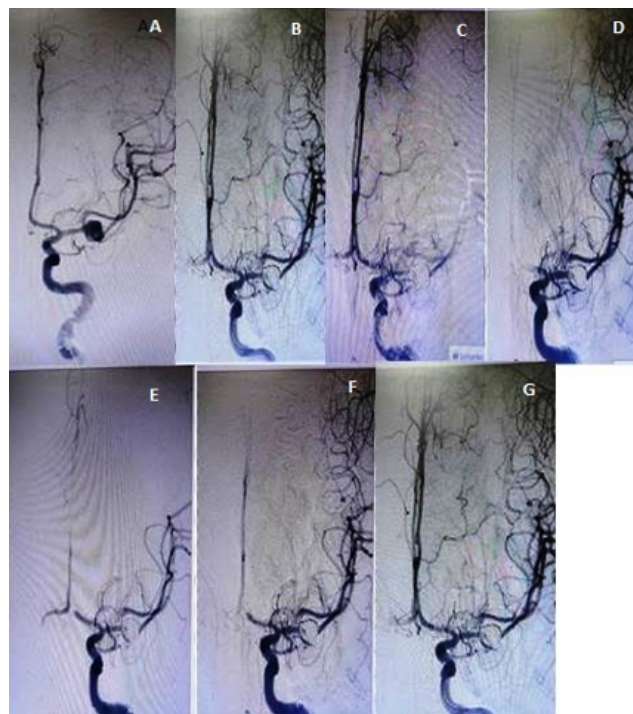
neurological grade and presence or absence of intra-procedural complications mainly.

1. NR phenomenon was defined as: Angiographic evidence of no flow of dye in small to large segmental portion of large and medium sized artery or arteries despite no evidence of dissection, spasm, stenosis or thrombus. Earlier the flow of dye was present without delay before quick development of this phenomenon.

The main inclusion criteria were patients with ruptured or unruptured aneurysms undergoing endovascular procedure in neurosurgery cath lab between march 2017–march 2021.

Clinical outcomes immediate post-procedure and at discharge were recorded. Angiographic findings were noted at the onset of NR and after management of NR.

Pre-procedure GCS and other neurological status were compared with post-procedure GCS and other neurological status.



**Fig. 1:** A): demonstrate medium size MCA aneurysm, next image; B): shows aneurysm tightly packed with coils. Further images; C-F): depict serial development of no flow/ no reflow, immediately after coiling procedure, meanwhile pharmacological measures were taken to abolish NR phenomenon. And finally; G): in the last image we were successful in restoring the flow in both MCA and ACA. Post-intervention the patient developed right hemiparesis which was gradually resolving with conservative management.

## 3. Results

The study enrolled 153 patients (72 male, 81 female) with a mean age of 56 years (range 34–78 years). NR

phenomenon was reported in 11 cases (7.2%) and occurred during catheter and wire navigation, during coiling stenting or immediately post-coil/stent placement

Following stent/flow diverter 6 (54.54%), after stent/flow diverter with coil 3(27.27%) and after coil placement 2(18.18%).

The clinical characteristics of those developing NR were explored compared with the control group (those who did not develop NR).

The former group was an older population with increased medical history of hypertension and presented with higher systolic blood pressures. Patients with NR had a delay across all recorded timings related to symptom onset and clinical interventions, when compared with the patients who did not. NR group included patients with obesity, DM, arteritis, multiorgan and multicentric arteriopathy, dyslipidemia, autoimmune diseases.

Analysis of the angiographical images demonstrated that the culprit vessel/vessels including parent vessel was abnormal angiographically with irregularity and stenosis. Difficult access, hardware reuse, complex pathology requiring more than simple coiling, requirement of multiple maneuvers and time taking procedures were all related with occurrence of NR.

Baseline flow was not reduced but post-procedure flow was significantly reduced, often absent (TICI 1 or 2a)

Patients in NR group had longer time to access the pathology with more efforts and unusual methods. More hardware's were used in NR group. More metal in the form of multiple coils balloons and larger stents were used in NR group

Patients with NR had increased risk of in-hospital death and disability (1 patient/9.1% death, 8 patients/72.72% with one or multiple neurological dysfunction with varying severity) in comparison to patients without NR(4 patients/2.8% deaths and 12 patients/8.5% disabilities, out of 142 patients).

#### 4. Discussion

NR is a segmental phenomenon rather than focal. It have patient related risk factors as well as procedure related risk factors. Thus identifying high risk patient and adapting different interventional strategy may alter the outcome. Though large number multicentric trial is needed to draw a statistical conclusion. A lot of cardiology literature is available about no-reflow phenomenon but not in neuro-endovascular literature. This phenomenon have peculiar presentation and specific management strategy. Awareness among neuro-endovascular surgeons is necessary. If the intra-procedural NR is left unmanaged, the outcome is not favourable often. So sensitization towards recognizing NR and immediate management is necessary. High risk group identification is also necessary. By recognizing high risk group of patients and procedures, we can do pre-

conditioning, post-conditioning and adaptation of safer interventional strategy. Also further research is needed for the management strategy of NR. Current main stay of management are beta blockers (metoprolol), vasodilators (nimodipine, sod. nitroprusside, nicorandil, nicardipine, verapamil), adenosine, Gp 2b/3a inhibitor, P2Y12 inhibitors and cyclosporine A. In authors' experience steroid is also beneficial.

NR is not a problem of canalization but it is a problem of flow. Dye don't flow across the segment in question and hence the blood but wires and catheters can be passed in the segment although it is not advisable and it is better to abandon the procedure after managing NR in authors' opinion.

NR starts with endothelial damage by mechanical shearing, hypersensitivity or ischaemia. After this there is endothelial swelling, neutrophil and platelet aggregation, vasospasm, and endothelial leakage. The cut-off margin during angiography in NR is abrupt and sharp with no filling defect and abnormality in margin. There are literature and evidences that endothelial hypersensitivity and inflammatory cascade spread through tight endothelial junctions to neighboring areas and the phenomenon becomes segmental.

There is scope of future research in the form of causative and risk factor validation, NR in neuro-endovascular surgery, exact pathophysiology of NR and pharmacological treatment.

#### 5. Conclusion

NR is a rare but unfavorable complication during neuro-endovascular surgery. Difficult access to pathology manipulation and maneuvering and heavy implantation in the form of coils and stents as well as patient factors appear responsible for its causation. Although multicenter large number studies and further research is required.

#### 6. Conflict of Interest

The authors declare that there are no conflicts of interest in this paper.

#### 7. Source of Funding

None.

#### References

1. Niccoli G, Burzotta F, Galiuto L. Myocardial no-re ow in humans. *J Am Coll Cardiol.* 2009;54(4):281–92.
2. Von EE, Altman DG, Egger M. Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Br Med J.* 2007;335(7624):806–14. doi:10.1136/bmj.39335.541782.AD.
3. Gurbel PA, Bliden KP, Butler K. Response to ticagrelor in clopidogrel nonresponders and responders and effect of switching therapies: the respond study. *Circulation.* 2010;121(10):1188–99.

4. Gremmel T, Eslam RB, Koppensteiner R. Prasugrel reduces agonists' inducible platelet activation and leukocyte-platelet interaction more efficiently than clopidogrel. *Cardiovasc Ther.* 2013;31(5):40–5. doi:10.1111/1755-5922.12021.
5. Galasso G, Schiekofers S, &anna D, C. No-Re flow phenomenon: pathophysiology, diagnosis, prevention, and treatment. A review of the current literature and future perspectives. *Angiology.* 2014;65:180–189.
6. Rezkalla SH, Kloner RA. Coronary no-reflow phenomenon: from the experimental laboratory to the cardiac catheterization laboratory. *Catheter Cardiovasc Interv.* 2008;72(7):950–7. doi:10.1002/ccd.21715.
7. Niccoli G, Kharbanda RK, Crea F, Banning AP. No-reflow:again prevention is better than treatment. *Eur Heart J.* 2010;31(20):2449–55. doi:10.1093/eurheartj/ehq299.
8. Weis SM, Cheres DA. Pathophysiological consequences of VEGF-induced vascular permeability. *Nature.* 2005;437:497–504.
9. Topol EJ, Yadav JS. Recognition of the importance of embolization in atherosclerotic vascular disease *Circulation.* *Circulation.* 2000;101(5):570–80.
10. Korybalska K, Pyda M, Kawka E, Grajek S, Breborowicz A, Witowski J, et al. Interpretation of elevated serum VEGF concentrations

in patients with myocardial infarction. *Cytokine.* 2011;54(1):74–8. doi:10.1016/j.cyto.2011.01.003.

### Author biography

**Kuldeep Yadav**, Associate Professor  <https://orcid.org/0000-0001-7710-1254>

**Deepak Kumar Singh**, Professor

**Mohd. Kaif**, Associate Professor

**Diwakar Shankar**, Senior Resident

**Cite this article:** Yadav K, Singh DK, Kaif M, Shankar D. No-Reflow phenomenon in the perspective of endovascular neurosurgery. *IP Indian J Neurosci* 2021;7(3):203-206.