msj Medicine & Science Journal

Medicine & Science Journal 2024; 2(1):e202448
https://doi.org/10.53150/2024.v2.48

LETTER TO EDITOR AND EXPERT COMMENTARY

Ranolazine for cardiac arrest: moving from *ex vivo* studies to clinical relevant *in vivo* models

Francesca Fumagalli, MBiol, PhD[1]; Marianna Cerrato, MBiol[1], Francesca Motta, MBiol[1], Daria De Giorgio, MBiol[1], Giulia Merigo, MBiol[2], Aurora Magliocca, MD,PhD[2], and Giuseppe Ristagno, MD,Ph[2, 3]

[1] Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy
[2] Department of Pathophysiology and Transplantation, University of Milan, 20122 Milan, Italy.
[3] Department of Anesthesiology, Intensive Care and Emergency, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, 20122 Milan, Italy.

Address for correspondence:
Francesca Fumagalli, MBiol, PhD
Department of Acute Brain and Cardiovascular Injury
Istituto di Ricerche Farmacologiche Mario NegriIRCCS
Via Mario Negri 2 - 20156, Milan, Italy
Tel. +39 02 39014622;
Fax +39 02 33200049
Email. francesca.fumagalli@marionegri.it

After successful cardiopulmonary resuscitation (CPR), approximately 70% of patients die prior to hospital discharge, mainly due to post-resuscitation myocardial and cerebral dysfunction [1]. Premature ventricular beats and life-threatening episodes of ventricular tachycardia and ventricular fibrillation (VF) commonly occur during the early minutes after resuscitation. Furthermore, an overall condition of severe myocardial dysfunction, including variable degrees of systolic and diastolic impairment, is present. Among the mechanisms underlying early post-resuscitation arrhythmia and myocardial dysfunction, cytosolic and mitochondrial calcium (Ca2+) overload have been recognized as a pivotal factor [2].

In a landmark randomized placebo-controlled trial, the Ranolazine Implantable Cardioverter-Defibrillator (RAID) published on JACC Clin Electrophysiol, Younis et al. [3] demonstrated that ranolazine, a drug commonly prescribed for the treatment of chronic stable angina pectoris, reduces the recurrence of ventricular tachycardia (VT) requiring implantable cardioverter-defibrillator (ICD) therapy. A study involving 1,012 patients identified seven factors associated with increased VT burden, including age ≥65 years, history of VT, and atrial fibrillation. Ranolazine significantly reduced VT burden in patients not on concomitant anti-arrhythmic drugs and those with cardiac resynchronization therapy ICDs [3]. This effect was elegantly explained as an improved dysregulation of intracellular Ca2+ accomplished by ranolazine through the sodium (Na+) current inhibition during VF. Based on these results, the potential therapeutic use of ranolazine

Received: August 2, 2024
Revised: August 17, 2024
Accepted: November 22, 2024
Published: December 20, 2024

Article information are listed at the end of this article.

in the setting of cardiac arrest (CA) is suggested, and testing in specific in vivo models is advocated.

We also support the potential role of ranolazine in improving the outcome of VF in terms of successful termination of the malignant arrhythmia and post-resuscitation myocardial dysfunction by blocking the Na+-dependent intracellular Ca2+ overload [4]. Starting from this hypothesis, in 2015 we investigated the effects of ranolazine in a rat model of VF, demonstrating for the first time that this drug was able to improve CA outcomes [5]. Indeed, ranolazine significantly improved defibrillation outcome, assessed by amplitude spectrum area, and reduced of almost 60% early post-resuscitation arrhythmias with hemodynamic instability. Finally, ranolazine significantly improved both post-resuscitation left ventricle (LV) systolic and diastolic dysfunction and survival. Despite these enthusiastic results, the potential of ranolazine as a future therapeutic option for CA remains to be determined. In fact, in our study, the drug was administered as a pretreatment, i.e. before the induction of VF [5]. This approach was selected to ensure ranolazine delivery to the myocardium before circulatory arrest; however, it limited the extrapolation of results to the clinical setting. We are now performing new studies with the same rat model of CA but with a more clinically relevant design, including the administration of ranolazine after resuscitation. Surprisingly, the preliminary results disagree with the earlier benefits observed with the pretreatment, showing an abruptly increased mortality when ranolazine is administered early after resuscitation. A severe hypotension, not observed in the instance of pretreatment, seems to be the most likely cause of such deaths.

Thus, further studies are needed to prove ranolazine's real benefits and elucidate the mechanisms of cardioprotection and potential adverse effects, as recently observed by our group. For these reasons, the clinical application of ranolazine in the treatment of VF cardiac arrest is still far away.

References

1. *Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al.: American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2019 update: a report from the American Heart Association. Circulation 2019;139:e56–e528. [Published erratum appears in Circulation 141:e33.]*
2. *Gazmuri RG, Radhakrishnan J: Protecting mitochondrial bioenergetic function during resuscitation from cardiac arrest. Crit Care Clin 2012; 28:245–270.*
3. *Younis A, Goldenberg I, Farooq S, Yavin H, Daubert J, Raitt M, Mazur A, Huang DT, Mitchell BL, Rashtian MR, Winters S, Vloka M, Aktas M, Bernabei MA, Beck CA, McNitt S, Zareba W. Reduction in Ventricular Tachyarrhythmia Burden in Patients Enrolled in the RAID Trial. JACC Clin Electrophysiol. 2022 Jun;8(6):754-762. doi: 10.1016/j.jacep.2022.02.018. Epub 2022 Apr 27. PMID: 35738852; PMCID: PMC9473303.*
4. *Dhalla AK, Wang WQ, Dow J, Shryock JC, Belardinelli L, Bhandari A, Kloner RA: Ranolazine, an antianginal agent, markedly reduces ventricular arrhythmias induced by ischemia and ischemia-reperfusion. Am J Physiol Heart Circ Physiol 2009; 297:H1923–H1929. 20*
5. *Fumagalli F, Russo I, Staszewsky L, Li Y, Letizia T, Masson S, Novelli D, Rocchetti M, Canovi M, Veglianese P, Gobbi M, Latini R, Zaza A, Ristagno G. Ranolazine ameliorates post-resuscitation electrical instability and myocardial dysfunction and improves survival with good neurological recovery in a rat model of cardiac arrest. Heart Rhythm. 2014; 11(9):1641-7.*