Editorial

Anti-arrhythmics in out-of-hospital cardiac arrest: lessons from a randomized controlled trial

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In a randomized double-blind trial, Kudenchuk *et al*. (1) assessed the effectiveness of amiodarone lidocaine or placebo for out-of-hospital cardiac arrest (OHCA) due to shock refractory ventricular fibrillation (VF) or pulseless ventricular tachycardia (PVT). The main objective was to compare the survival hospital discharge between amiodarone recipients versus placebo recipients. Secondary comparisons for survival outcome have been realized for the patients between the groups "*lidocaine versus placebo*" and between the groups "*amiodarone versus lidocaine*". The secondary outcome was the favorable neurologic function at discharge. Study outcomes was assessed in two populations: an efficacy or "modified intention to treat" population and a safety or "intention to treat decision" population. From May 2012 to October 2015, the Resuscitation Outcomes Consortium (ROC), a North American multicenter network with an emphasis on prehospital trials, has treated 7,051 shock refractory VF or PVT. Of these, 3,026 have benefited from the modified intention to treat analyses. In the amiodarone group, 24.4% survived to hospital discharge versus 23.7% in the lidocaine group and 21% in the placebo group. Neither of the two anti-arrhythmic did better than placebo (respectively P=0.08 and P=0.16) and the main outcome did not differ between amiodarone and lidocaine (P=0.70). However the study suggests that the survival could be improved by amiodarone administration versus placebo, in the particular case of bystander witnessed OHCA (P=0.01).

OHCA is a major public health problem, both in the United States and Europe. In previous decades, the majority of writers associated with the work Kudenchuk *et al*. (1) had already contributed enormously to improving the prognosis of OHCA. It is now 25 years ago that Cummins modeled the chain of survival, describing the actions linking the victim of sudden cardiac arrest with survival. These actions include early recognition of the emergency and activation of the emergency services, early cardiopulmonary resuscitation, early defibrillation and early advanced life support (2). Furthermore they demonstrate the necessity of limiting the delays of intervention in order to improve the survival.

Upon the arrival of the emergency team, OHCA are divided in two alternatives in terms of heart rhythms. The rhythms shockable with an Automated External Defibrillator (AED) are VF and PVT. Non-shockable rhythms are asystole and pulseless electric activity (PEA). The survival rate of VF and PVT is far superior to other rhythm disturbances. The only treatment available for VF/PVT is electric shock (ES) administrated by a defibrillator. Currently it can be administrated by all lay person thanks to public AED. The efficiency of the first ES is higher than the following, and the earliest it's administered (3,4). The efficiency is defined by a loss of VF, the onset of PEA, and at best, a return of spontaneous circulation (ROSC). The availability of defibrillators to non-physician professional rescuers and then a wide dissemination to the general public were the most important therapeutic advances in the treatment of OHCA since the invention of CPR. VF, however, has a bad tendency to persist and the need for additional shock quickly reduces the chances of survival (5). Among persistent VFs, we must distinguish on the one hand resistant VFs that are defined by their persistence to the 5th second post-shock; and on the other hand, recurrent VFs that disappeared immediately post-shock

but later reappear. To permanently resolve a VF/PVT, the guidelines suggested since 2005 were to combine injectable amiodarone after the 3rd ES and the administration of epinephrine. For second attempt, lidocaine was suggested (6).

What knowledge do we have of these two anti-arrhythmics? Amiodarone blocks sodium, calcium and potassium channels. If the blockage of the sodium and calcium channels increases the energy required for defibrillation, just the opposite, the blockage of potassium channels reduces the defibrillation threshold. Because of individual differences in ion channel sensitivity, amiodarone can have a very different effect on the defibrillation threshold in terms of individuals (7). This drug exists in two injectable forms that differ in their solvent. Polysorbate 80 (PS80), which is the traditional solvent, has a hypotensive effect. Captisol, a solvent available since 2010, is hemodynamically inert. Both previous studies (8,9) on the effect of antiarrhythmic drugs in OHCA with shock resistant VF/PVT, and which served as support for the 2005 Guidelines, were still using PS80. The first of these two studies (8) reported a superiority of amiodarone versus placebo with the "proportion of patients who survived upon being admitted to the hospital" as primary endpoint. The second study (9) reported a superiority of amiodarone versus lidocaine in terms of survival at hospital admission. In these two randomized controlled studies, the control group had been administering the PS80 solvent to reduce the risk of hypotension in the two groups at the same level. Kudenchuk's study (1) is the first that uses Captisol.

Lidocaine is a membrane stabilizer that increases the refractory period of myocytes. This molecule blocks sodium channels and causes a reversible, concentration-dependent increase in defibrillation energy requirements (10).

No study had ever tested these molecules versus placebo in OHCA to verify a possible superiority in terms of leaving the hospital alive (11). This was Kudenchuk *et al*. study's main objective (1). The methodology of this work was described in a previous publication (12). Should recently published results, which we briefly summarized at the top of this page, lead us to conclude the lack of antiarrhythmic drugs' efficacy in OHCA? The means that were invested in this work are extremely important. Despite this, the authors explain that the trial may have been underpowered and treatment administration remained too late compared to the moment of the OHCA's occurrence.

We should ask how such a well-designed study could result in an underpowered trial. One explanation lies in the fact that the calculation of the required number of subjects was made by taking into account the parameters of studies on the same topic more than 10 years before (8,9,12). Yet the management of OHCAs was significantly different and the survival chain less efficient. In 2016, the time devoted to external cardiac massage (the "chest compression" ratio) was measured by Kudenchuk *et al*. with formidable precision and reports a high quality of lifesaving services thanks to feedback in real time. This feedback was not achieved in previous studies. Another point concerns the defibrillation protocol. Before 2005, this protocol called for three consecutive shocks in case of persistent VF. After 2005, the "single-shock" strategy was recommended (13). The AEDs and manual defibrillators used in Kudenchuk's study in 1999 issued monophasic shocks, while in 2016 they all deliver biphasic shocks. However, biphasic waveforms have reduced the risk of persistent VF by up to 81% compared to monophasic waveforms of the same energy (14). The cohort of patients treated in 2016 for persistent VF after three single biphasic shocks is a cohort that has undergone a much greater selection pressure before any administration of amiodarone than the previous cohorts who had been treated with three successive monophasic shocks. Kudenchuk could hardly consider this particular point at sample size calculation.

What about the administration time of anti-arrhythmics? During an OHCA, these treatments have less impact the later they occur in the course of the chain of survival. Weisfeldt has developed the 3-phase model of cardiopulmonary resuscitation to reflect the time-sensitive progression of resuscitation physiology (15). The model proposes a first electrical phase (from the time of occurrence of the OHCA until the 4th minute), a second circulatory phase (from approximately the 4th to the 10th minute) and a metabolic phase, after the 10th minute after the collapse. If we observe the injection times of antiarrhythmic treatment in the various tests (8,9,12), unfortunately they always correspond to the establishment of the metabolic phase of the cardiac arrest, that is to say, a phase during which the behavior of ion channels could only be altered, resulting in limited drug action compared to its expected effect.

How to save time? The antiarrhythmic agent is part of the therapeutic arsenal deployed by the "Advanced Live Support" (ALS) teams. In a two-tier backup system (Basic Live Support—BLS teams, followed by ALS teams), it encourages us to reflect on the possibility of developing the drug in a galenic form (sublingual or intranasal) that would be administered by the first responders, namely the BLS

teams. The administration would take place as called for in the recommendations after the 3rd AED shock without ROSC. While many will have obvious difficulties with this idea, we think it is an interesting point to ponder. In the short term, we admit this perspective is still out of reach. It will require a revolution in the organization of the chain of survival in due course.

Can we hope, by then, for the validation of another antiarrhythmic agent that would be capable to meet the metabolic demands of the late phase of its administration? Who would dare to restart a randomized controlled trial as heavy as the one we are considering in these pages?

What are the therapeutic alternatives currently at our disposal to better manage persistent VF? Remember, an OHCA supported with AED only benefits from a rhythm analysis every 120 seconds. Yet, an observational study reported that 80% of instances of recurrence occurred before the 60th second and 52% in the first 30 seconds post-shock (16). Time to recurrence of VF seemed to be a constant. Given these results, in the current situation, a persistent VF lasts about 1 minute of waiting and additional chest compressions before being identified and shocked. To correct this, it would involve setting up an AED analysis algorithm that knows to ignore the signal related to chest compressions to detect VF recurrence as soon as it appears. If some devices today offer this possibility, we must further improve the ability to discriminate VF from chest compression signals. The validation of VF requires a clean signal that is only obtained with CPR interruption. The result is an increase in hands-off time. Associated with easy to administrate anti-arrhythmic drugs, could it be our future of OHCA early treatment?

Finally, an important point is the search for causes of the occurrence of refractory VF. If chest compressions themselves can promote refibrillation (17), the underlying pathology is likely to play an essential role.

At the end, Kudenchuk's study, with little to criticize in terms of methodology, complements the many negative OHCA studies during the last decade (18), whether they're studies on medical devices or drug treatments. However, one can be optimistic when we see that between 2002 and 2016, the rate of survival at hospital admission was doubled for patients treated with amiodarone and tripled for those treated with lidocaine (8,9,12).

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