To interrupt, or not to interrupt chest compressions for ventilation: that is the question!

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Out-of-hospital cardiac arrest (OHCA) is one of the leading causes of death in the industrialized world, with an average global incidence of 55 cases per 100,000 person-year (1). OHCA is a major public health problem. Every 5 years leading institutions like the European Resuscitation Council (ERC) and the American Heart Association (AHA) publish the resuscitation guidelines, with treatment recommendations for OHCA based on a comprehensive review of the available scientific evidence. Despite the therapeutical advances introduced by the guidelines over the years survival remains dismally low, with average survival rates to hospital discharge below 6% for all cases, and below 12% for patients presenting initial shockable rhythms (1).

Quality cardiopulmonary resuscitation (CPR) is critical for the survival of the patient suffering OHCA. During CPR chest compressions are delivered in the center of the chest, with target depths of 5–6 cm, rates of 100–120 min^{-1} and allowing complete chest recoil. Since the 2005 update, resuscitation guidelines recommend a sequence of 30 compressions followed by a 5-s interruption for 2 ventilations, the standard 30:2 CPR. During CPR chest compressions are interrupted for various reasons including rescue breaths, rhythm analysis, pulse-checks and defibrillation. These interruptions decrease coronary and cerebral blood flow and have been associated with decreased survival both in animals and humans (2-4). Rescue breaths are critical in respiratory arrest, where hypoxia leads to cardiac arrest. In nonasphyxial arrest arterial blood is saturated with oxygen for several minutes, and rescue breaths may not be essential for survival (2,3). During the circulatory phase of the arrest (4–10 min from arrest), the generation of adequate cerebral and coronary perfusion by chest compressions maybe crucial for the survival of the patient (5). This observation leads to the introduction of the concept continuous chest compressions (CCC), i.e., CPR without pauses for ventilation.

Researchers from the University of Arizona in cooperation with the Tucson Fire Department instituted the basis of cardiocerebral resuscitation (CCR). CCR is an alternative to the standard resuscitation protocol that emphasizes the adoption of CCC. They proposed a bundle of treatment changes including 200 uninterrupted preshock chest compressions, rhythm analysis with a single shock, 200 immediate postshock chest compressions before pulse check or rhythm reanalysis, early administration of epinephrine and delayed endotracheal intubation. They first introduced CCR in 2005 in selected emergency medical services (EMS) (6-8), progressing up to larger observational cohort studies and prospective studies with historical controls (9-11). In their largest study involving 2,460 patients (10) the adoption of CCR in EMS systems almost tripled overall survival to hospital discharge from 3.8% to 9.1%, an effect observed also in patients with witnessed ventricular fibrillation (from 11.9% to 28.4%). The increase in survival rates was due to a multiplicity of factors associated to the bundle of treatment changes introduced by CCR, and may have also been due to improved CPR quality. Unfortunately CPR quality data was not recorded in these studies.

One of the advantages of CCC is the increase of bystander CPR rates, because many bystanders are unwilling to give mouth-to-mouth rescue breathing (12). However, once CPR is initiated by the bystander the advantages of CCC over standard CPR are unclear. Several Japanese studies have investigated the effect on survival of both types of CPR. These observational studies ranged from the initial local retrospective studies of under 5,000 cases (13,14), to

nationwide prospective studies of about 50,000 cases (15,16). Bystander CPR increased survival when compared to no CPR, however no significant differences in survival with good neurological outcome were found between standard and compression only CPR. In fact, for non-cardiac arrests standard CPR was superior to compression only CPR. For arrests of cardiac origin both types of bystander CPR had comparable survival rates—6.4% *vs.* 7.1%—when CPR was delivered before 15 min, but survival was significantly higher for standard CPR—2.0% *vs.* 1.3%—when CPR was initiated after 15 min.

Increasing bystander CPR rates through the use of simplified protocols such as CCC may lead to higher survival rates (12). However, the benefits of CCC over the standard 30:2 protocol for CPR delivered by EMS services are unclear, so current ERC guidelines still recommend 30:2 CPR (17,18). The bundle of therapies introduced in the studies advocating the use of CCR result in many confounders that mask the contribution to survival of individual therapies such as CCC. The contribution to survival of CCC is further obscured by the absence of CPR quality data in these observational studies with historical controls. The study by Nichol *et al.* (19) finally sheds light on whether CCC as compared with the standard 30:2 protocol improves survival when CPR is delivered by EMS providers.

The study was designed as a crossover cluster-randomized control trial (RCT) of non-trauma related cardiac arrest treated by EMS (20), and was conducted by the resuscitation outcomes consortium (ROC). The primary outcome was the rate of survival to hospital discharge, with neurologic function at discharge as secondary outcome. The trial involved 114 EMS agencies from 8 ROC sites grouped in 47 clusters during a period of 4 years. The clusters were crossed over twice a year between the two resuscitation strategies, namely CCC (intervention group) or the standard 30:2 protocol (control group), designated as interrupted chest compressions (ICC). Patients assigned to the CCC group were to receive compressions at a rate of 100 min^{-1} with positive-pressure ventilations at a rate of 10 min^{-1}. For the patients in the ICC group pauses for two ventilations were to last less than 5 s. In total 12,613 patients were assigned to the intervention group (CCC) and 11,058 to the control group (ICC), and in both cases primary outcome data was available in more than 99.7% of cases.

The study sites acquired and reported CPR-quality data measured by the monitor-defibrillators which included variables such as rate, depth or chest compression fraction (CCF). These data was reviewed by an automated algorithm and by the research coordinator to ensure adherence to the treatment protocols, and a per-protocol analysis of the data was then conducted. The per-protocol analysis based on the automated algorithm included 6,529 and 3,678 patients in the intervention and control groups, respectively.

The characteristics of the patients, EMS providers, and hospital treatments were well balanced between the two branches of the trial. There were of course significant differences in the CPR data related to pauses in chest compressions, with significantly higher CCF (0.83 *vs.* 0.77) and less pauses in compressions (3.8 *vs.* 7.0) in the intervention group. Although significant, these differences were not as large as expected because rescuers did not strictly adhere to the treatment protocol. In the per-protocol analysis differences were much larger (0.87 *vs.* 0.73 for CCF, and 2.8 *vs.* 10.3 in number of pauses), but some pretreatment and treatment characteristics were imbalanced, with significantly higher rates of shockable rhythms and prehospital intubations in the control group.

Nichol *et al.* found no significant differences in survival to hospital discharge between the CCC and ICC groups, with survival rates of 9.0% and 9.7%, respectively. Differences in survival with good neurological outcome, defined as score of three or less in the modified Rankin scale, were also not significant with values of 7.0% in the intervention and 7.7% in the control group. In the per-protocol analysis, which ensured adherence to the treatment protocol, survival was significantly higher in the control group, with rates of 9.6% and 7.6% for the ICC and CCC groups, respectively. However, when adjusted for pretreatment confounders differences in survival rates in the per-protocol analysis were no longer significant.

Two key factors explain these results. First, by conducting a large scale RCT Nichol *et al.* were able to isolate the effect on survival of pauses for two rescue breaths, particularly in the per-protocol analysis. In contrast, previous studies introduced a myriad of changes in the treatment protocol which obscured the contribution to survival of individual treatment changes. Second, CPR quality in both branches of the trial was close to optimal, with rates around 110 min^{-1}, depths close to 50 mm and CCF above 0.7. All these CPR quality variables have been previously shown to influence survival and were not controlled for in the previously cited studies. One of the limitations of the study is the small difference in CCF between the treatment branches. However, when adherence to treatment protocols was checked differences in CCF were larger.

The study by Nichol *et al.* shows that pauses for two rescue breaths in 30:2 CPR are not detrimental for survival, even when the presumed cause of the arrest is cardiac.

This is particularly so when CPR is delivered in the ranges recommended by the resuscitation guidelines.

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