Reinforcing the Links in the Chain of Survival

Pier Lambiase MD PhD FRCP FHRS

Institute of Cardiovascular Science, UCL & Barts Heart Centre
Cardiology Department
St Bartholomews Hospital
West Smithfield
London EC1A 7BE

p.lambiase@ucl.ac.uk

Tel & Fax: +44 203 357 1319

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Out-of-hospital cardiac arrest (OHCA) affects 235,000–325,000 people in the United States, 275, 000 in Europe, each year. However, the survival rate after OHCA, especially without neurological impairment, remains low[1-4]. Every minute without CPR and defibrillation reduces the chances of survival by 7- 10%. Isovolumic left ventricular developed pressure falls by more than 50% within 30 seconds of the onset of total global ischemia reaching zero by 5 minutes demanding effective defibrillation to be delivered within 5minutes to significantly affect outcomes[5].

In order to address this, the AHA recommended a “chain of survival” concept consisting of the following *5 links*: 1. Early access to emergency medical care 2. Early CPR 3. Early defibrillation 4. Early ACLS 5. Expert post-resuscitation medical care[3].

These links must be seamless but there is huge variation in delivery. The emergence of public access automatic defibrillators (PADs) has made a significant impact on the first 3 links in the chain.

A recent study, in Japan, demonstrated that the proportion of PADs use significantly increased from 0.0% in 2005 to 41.2% in 2011 at railway stations and from 0% to 56.5% at sports facilities. Mean time from collapse to shock was 5 minutes among those who received shocks with PADs. 28.0% had a favorable neurological outcome at railway stations, 51.6% at sports facilities, 23.3% in public buildings, 41.9% in schools. In multivariate analysis, early defibrillation, irrespective of bystander or EMS personnel, was significantly associated with good functional outcome (adjusted odds ratio for 1-minute increment, 0.89)[6]. Therefore rapid use of PADs could have a major clinical and socio-economic impact on OHCA outcomes before one engages the more sophisticated & resource intensive processes required in the 5th link -*the subject of Yannopoulos et al*. This requires not only deployment of PADs universally in public areas and easy accessibility but training the general public in basic CPR & PAD use to ensure immediate shock deployment. Numerous strategies are being explored including utilization of smart phone apps to localize PADs and even drones to deliver them more immediately[7]. However, 80% of cardiac arrests occur at home in lone individuals meaning that "wearables" and smart clothing to monitor physiology e.g. Fitbit® watches have potential to issue an emergency call in the event of cardiac arrest. This demands highly reliable detection of haemodynamically compromising arrhythmias with technology to verify haemodynamic collapse (positional information, tissue perfusion) and wearer interaction to prevent devices "crying wolf" overwhelming emergency services.

Yannopoulos et al have concentrated on the 5th link in the chain- in the rare but potentially reversible scenario of refractory VF occurring in 0.9% of all cardiac arrests[8]. The study required impressive engagement of EMS, specialized cardiac & ITU teams to ensure a highly choreographed delivery of continuous external automated mechanical CPR, extracorporeal life support (ECLS) & coronary intervention achieving phenomenal 6min door to ECLS initiation & 12min door-balloon times. The authors & medical teams involved are to be applauded for this unprecedented achievement. The strategy resulted in 42% of patients leaving hospital with a high level of neurological function versus 15.3% of historical controls. These outcomes compare favorably with the SAVE-J and CHEER trials of 29% and 45% survival to hospital discharge which also utilized ECLS & coronary intervention in resistant VT/VF[9,10]. To put these figures in context, a Japanese study focusing on ROSC triaged cases transferred to tertiary centres for therapeutic hypothermia & coronary intervention only achieved a 1 month neurologically intact survival of 3% versus 0.5% in historical controls, highlighting the potential benefit of very early coronary intervention[11].

A number of caveats should be highlighted in *Yannopoulos et al*. As an observational study there are confounding biases of subject selection and comparison with historic controls where inclusion criteria promoting greater probability of survival could not have been as strictly applied. However, it is interesting to note that in this historic control group, ROSC on arrival was more 4 times common (c.38% vs 9% fig 3) indicating that these patients were in a better condition & yet had worse survival. Important critical differences being lack of ECLS and coronary intervention, although they were not matched for burden of coronary disease, co-morbidities & baseline ejection fraction. Furthermore, key significant determinants of survival in the treated group were only a 3min difference in first response arrival (4.1min v 7.1min) again highlighting the time criticality of effective CPR. The presence of intermittent ROSC before arrival and the presence of CAD as survival predictors identify the prevalence & importance of a treatable reversible cause with 84% receiving PCI.

A significant source of complications was ECLS-13% of patients had vascular complications including retroperitoneal bleeding & leg ischemia. This is in line with the most recent meta-analysis of ECMO- 27% major bleeding, 8%. thromboembolic events - limb ischemia, circuit-related clotting, and stroke[12]. Optimization of circulatory support requires new approaches to avoid full anticoagulation e.g. anti-thrombotic circuit materials and cannula re-design to prevent vascular complications.

Despite over 40 years of work in the field of cardioprotection, only the re-establishment of perfusion has been shown to significantly impact survival in acute coronary occlusion[13]. Indeed during the first few minutes of refractory VF profound ischaemia induced electrophysiological changes occur which can only be corrected by reperfusion. No drugs to date improve reversion rates and amiodarone (our most effective anti-arrhythmic) is suboptimal in this circumstance. This is especially important in the >80% of this study where ischaemia will persist without PCI despite CPR. Pharmacological pre-conditioning agents to reduce infarct size have not reached the burden of proof to enter clinical practice & have to be delivered prior to the initiation of infarction to enable protection, so are not applicable to reperfusion. This has lead to post-conditioning (interruption of reperfusion with short periods of ischaemia) or remote post-conditioning (e.g. using limb ischaemia with a blood pressure cuff as the stimulus) strategies to diminish the effects of metabolic and ionic changes & activate myocyte survival pathways thought to operate mainly by inhibiting the opening of the mitochondrial permeability pore[13]. However, the recent randomised controlled trial- ERICCA utilizing remote pre-conditioning in cardiac surgery failed to show any benefit in a combined primary end point of major adverse cardiac and cerebral events within 12 months[14]. Remote post-conditioning is currently being evaluated in ST elevation MI cases (RIC-STEMI-NCT02313961) and primary PCI (NCT00435266 -unreported despite completion in 2009 on *clinical trials.gov).*

While the authors are to be congratulated- currently, from a practical perspective, greatest gains will be from investment in ensuring immediate CPR & defibrillation in <5mins for the >0.5million cardiac arrests per annum in Europe & USA where numbers saved will be greatest (c.50,000 vs 450 lives with ECLS & PCI for refractory VF assuming only 20% are witnessed). Inevitably, as this improves, demand for optimizing the 5th link will increase but the priority should be links 1-3. Our challenge is to ensure that every dollar is spent to save the maximum number of lives when literally every minute counts.

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