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Can preconditioning, an ageing intervention, undergo anastasis?

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Keywords: Preconditioning myocardial; Infarct medications; Remodeling; Resurrection; Anastasis.**Abbreviations:** PC: Preconditioning; Post C: Postconditioning; SEVO: Sevoflurane; RIPC: Remote Ischemia Preconditioning; I/R: Ischemia/Reperfusion.

Preconditioning is ageing, but questions still remain

Preconditioning (PC) is a concept now 36 years old, since first described in 1986 by Murry et al in KA Reimer's laboratory [1]. Over the years a huge number of experiments, reviews and meta-analyses have been produced. Pre- peri- and post conditioning have been described together with direct and remote application [2]. Amazing insights dealing with functional, biochemical, molecular and genomic changes have emerged [3].

It is described as a universal phenomenon, effective in single cells, organs, whole organisms, and even observed in the plant world. Moreover, preconditioning mimetic drugs have emerged as will be further described. However, there is a flaw in the full moon. Currently, PC is not used clinically in any circumstances. It is not mentioned as an adjunct to other types of therapy against myocardial dysfunction and death, in any guidelines not

at best as a 2 level recommendation. It has become a pastime for the basic researcher, because clinical studies have actually been side shelved.

One of the reasons proposed to explain this lack of interest is that elective angioplasty and cardiac surgery have attained by now very low mortality and morbidity [4]. Thus any additional intervention will be difficult to show an improvement in invasive cardiology results. In this context, the dire emergency of primary angioplasty remains a viable option for PC to be applied.

McLeod et al found a higher salvage index and a reduced infarct size with RIPC application [5]. However, in the large and definitive DANAMI 3 trial which included 2 1234 pts local (direct) PC failed to show a benefit with 4 repeated balloon occlusions deflations [6]. Accordingly, in 2017 Lavi and Lavi advised that

post C was not yet ready for prime time in primary angioplasty [7]. They conclude that we may need to go back the drawing board and find new ways.

Another technique tried in this procedure is controlled reperfusion. Ma et al describe it in 2021 as, clinically occurring during recanalization treatment of ischemic organs [8]. However, they stressed that it needs control of reperfusion with blood and/or chemical compositions, rendering it too complicated. Post-C is usually applied immediately after reperfusion. However, Roubille et al [9] subjected mice to 40 min of ischemia and 60 min of reperfusion.

They showed that delaying post C up to 30 min did not abrogate its cardioprotective effect. This is an important finding, since apoptosis is a main feature of reperfusion injury in the setting of an acute infarct [10].

Direct PC has been tried in cardiac surgery but is difficult to apply in real life. In the chronic stage of cardiac remodeling Wei et al [11] have actually shown a decrease of post-infarct remodeling in rats with remote reperfusion, but this technique is very difficult to apply in humans for a month.

The volatile anesthetic concept- An application to be reconsidered in cardiac surgery

In this setting another proposed cause of neutral effects of PC, is that the volatile anesthetics which are widely used, provide significant cardioprotection by themselves which would cover the potential additional effect of PC [3].

However, Cho et al [12] believe that Sevoflurane (SEVO), propofol and carvedilol actually block this protection. Their study was performed clinically in pts undergoing cardiac surgery and experimentally in rats undergoing I/R. Remote PC (RIPC) was robust in the no-anesthesia or no-carvedilol group, but abolished in the drug receiving group. What was interesting however in these groups was that no cardioprotection was found, by any drug in the rat model, contrary to many reports 3 already mentioned. In the clinical group no difference in peak troponin or hospital stay was found.

A new question in this field has emerged over the years:

Should continuous SEVO PC still be used or, as it holds true for ischemic PC, should it be given in cycles? Conflicting studies are still being reported.

Wu et al [13] in pts with a history of myocardial ischemia undergoing abdominal surgery using a routine SEVO administration found a reduction of serum indices of cell death ischemia and inflammation. The same was seen in rats.

However, Guinot et al [14] in 81 pts undergoing cardiac surgery did not find any difference in cTnI kinetics or composite events, or GDF-15 elevation, an independent marker of mortality.

Riess et al [15] were the first to show that dual exposure to SEVO affords greater cardioprotection as compared to single dose in infarct pig hearts undergoing an experimental infarct.

Zhao et al [16] also used, 3 cycles of 10 min each of SEVO (again at 2% concentration); they found a 20.2% reduction of infarct size in wild type mice. These data suggest that repeated

doses of SEVO should be employed in the clinical and experimental setting from now on. As regards the clinical use, it is interesting to note that SEVO can also be used without intubation [17].

Thus, if one were to use a SEVO- protection protocol, our advice would be to go where the money is, use a double or triple PC stimulus.

It should be mentioned is that SEVO can also elicit cardioprotection both through pre and post conditioning, in the pig liver I/R [18], and in the rat heart as post C [19].

Thus, possibly a combination of SEVO pre-and post-conditioning given intermittently could be more efficacious. However all said, which would be the instances in which intermittent SEV pre- and post-conditioning could be further tried?

A prime model would be cardiopulmonary resuscitation in the human where results are still poor.

A second would be primary angioplasty in a big (LAD area) infarct. In this paradigm no additional cardioprotective intervention has proven of value, and left ventricular remodeling ensues in up to 30% of cases [20].

SEVO post C has been synergistically employed with RIPC in rats [21], in parallel way to combine ischemic pre and post C [22].

Candidate drugs to replace or complement PC

Obviously, SEVO cannot be given continuously, neither can opioids. Thus, other drugs that can elicit pharmaceutical PC are required in the practical area. Das and Maulik [3] have mentioned a large host of molecules, most of which cannot be employed clinically. Nitrates could be an agent, as shown by Leesar et al [23], more than 20 years ago. They are a widely used drug of families.

Nicorandil, a potassium channel opener has been used clinically, but has not secured a substantial niche, although it can affect both pre-and post C [24]. We have found that thyroid hormones have a PC like protective effect and prevent remodeling [25] but it is difficult to justify its use in euthyroid pts.

Herbal substances, such as curcumin [26] and resveratrol [27] are very popular in Asian literature but have not taken root in European soil.

Actually, combined ischemic pre C and Resveratrol interventions gave better results than either alone as regards improved blood brain barrier breakdown [27].

Erythropoietin has been proposed as a PC mimetic from basic science results [28] but neutral clinical results a few years ago, have disappointed clinically [29], and is no longer mentioned as a prospect. Thus more practical drugs are urgently needed. Some already widely used drugs have been shown to be effective. Thus PPARs [30] (α and γ) have shown neurological protection following ischemia reperfusion in rats. Statins are well known to improve cardiac function after ischemia-reperfusion [31]. High-dose statin pretreatment has an important effect on postprocedure myocardial perfusion by improving the TIMI flow in patients undergoing PCI, and high-dose statin preload-ing also reduces the incidence of MACE [32].

The new family of drugs PCSK9 inhibitors also have this effect beyond their lipid lowering effects [33]. They are obtaining wide use as lipid-lowering drugs, but the cardioprotective aspects against ischemia/reperfusion are beginning to emerge.

It should not be forgotten that these drugs have direct anti-apoptotic actions of their own [34]. Probably the family of drugs most widely studied currently are SGLT2 inhibitors. Beyond their glucose-lowering effect they have been found to be cardioprotective even in cell culture [35].

A recent study mentions that they may have a PC like effect on the reperfused ischemic heart [36].

Another aspect of PC should be considered: it is not only affected by different protocols i.e. time of application, cycles of ischemia reperfusion, in humans it is affected by age, heart failure, hyperlipidaemia and diabetes mellitus. Kleinbongard et al [37] have shown very recently that the Ossabaw minipigs with genetic predispositions to the metabolic syndrome are non-responsive to ischemic PC. The aforementioned new families of drugs PCSk9 and SGLT2 inhibitors could potentially reverse this predisposition.

These data bring into focus an up to now critical question: Are various interventions PC mimetic or just protective?

We believe that PC and other interventions mentioned are all constituents of the cardioprotective continuum rendering these distinctions obsolete.

Ischemic PC should not be forgotten despite the increasing application of drugs exercise PC should not be abandoned. We have shown by dual isotope scintigraphic studies the value of exercise induced PC [38]. Similar techniques could be employed by exercise to evaluate the contribution of additional drugs.

A look into the future

Cell death is up to now an irreversible process. In the last 10 years a new term “anastasis”, meaning rise from the dead -resurrection- in Greek has emerged, according to which apoptosis can be reversed [39]. PC should be investigated in this process. As already noted late post-conditioning has been demonstrated by some researchers [9]. Could these results represent another aspect of “anastasis”? Further research on this subject is necessary.

A final note should be added: It is not scientifically sound to only discuss the practical aspect of any research endeavors. Research should not necessarily have an aim. Blue skies, another word in basic research, can yield substantial contributions to our knowledge.

Thus, clinical application and pre-clinical research should go together, in a mutually helpful feedback cycle.

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