NITRIC OXIDE AND LOW PERFUSION STATES : MYOCARDIAL ISCHAEMIA AND SEPTIC SHOCK

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Any injury to a living organism triggers a response which is aimed to reestablish the homeostasis. This usually holds true when the magnitude of the insult is within the limits of the compensatory mechanisms. In such cases like myocardial ischaemia or septic shock, the seriousness of the challenge is beyond the limits of any salvage. In general, these two conditions can be classified under the term of "low-perfusion states" indicating that the tissue perfusion is highly impaired due to either total lack of blood flow or diminished because of the relative decrease in the amount of nutritive blood reaching the organs.

In both cases, various mechanisms are triggered and consequently, numerous mediators, having profound effects are released into the circulation (Table 1). It is believed that the most important final common target for both conditions is the failure of the vasculature which eventually leads to tissue hypoperfusion and mortality.

Catecholamines
Autocoids
Cytokines
Arachidonic acid metabolites
Adhesion molecules
Endothelin
Nitric oxide

Table 1 : Some mediators associated with low perfusion.

Recently, nitric oxide is suggested to play the central role in septic shock and in coronary ischaemia-reperfusion injury. Being a molecule possessing both beneficial and deleterious effects, it is difficult to establish the exact nature of nitric oxide-related events. However, in septic shock, there are some powerful evidence such as the elevation of cyclic GMP levels in tissues or beneficial effects of nitric oxide inhibition which strongly suggest that the increased production of nitric oxide is indeed responsible from the pathology. Although the beneficial effects of nitric oxide inhibition in sepsis-related events are still under debate, there exists a considerable amount of information regarding the pivotal role of nitric oxide in systemic inflammatory response syndrome-related pathologies.

On the other hand, the role of nitric oxide in myocardial ischaemia-reperfusion injury is still controversial. It is possible to come across reliable accounts which indicate that nitric oxide is beneficial while others reporting its deleterious role. Since the main reason of mortality from myocardial ischaemia-reperfusion is fatal arrhythmias, investigating the effect of nitric oxide on arrhythmogenesis appears to be the right appro-

Endotoxaemia	INSULT	Coronary Ischaemia
	↓	
Mediator release	RESPONSE	Mediator release
	↓	
Vascular damage	INJURY	Myocardial damage
	↓	
	TISSUE HYPOPERFUSION	
	↓	
	MORTALITY	

Table 2 : The role of nitric oxide in myocardial ischemia.

ach (Table 2). Therefore stimulating the production of nitric oxide in copious amounts via inducible nitric oxide synthase by using lipopolysaccharide and quantitating the arrhythmic activity seems feasible. Additionally, the usage of proper antagonists shown to inhibit the production of nitric oxide is also expected to further the understanding of the role of nitric oxide in these pathologies.

In an attempt to combine both of the abovementioned entities, we decided to administer Escherischia coli endotoxin to albino rats four hours before occluding their coronary arteries and investigated the arrhythmic outcome. Our results indicated that the animals which were treated with endotoxin, displayed less arrhythmic activity which we attributed to the stimulated production of nitric oxide. The blockade of the antiarrhythmic effect of endotoxin by known inducible nitric oxide synthase blockers like dexamethasone and L-canavanine has also supported our conclusion that the nitric oxide itself is indeed beneficial in myocardial ischaemia which may be further exploited for developing alternative treatment strategies.

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