EDITORIAL

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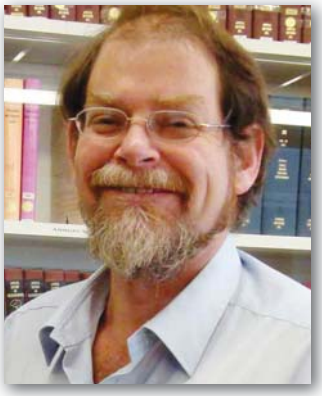

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SA cardiovascular laboratories mining diverse, yet relevant research topics

This issue of SA Heart reports on some ongoing work performed in South Africa that engages with more fundamental issues of the mechanisms of cardiovascular disease. This special edition of the journal highlights some of the high quality, internationally competitive, clinically relevant, basic cardiovascular science presently being undertaken by a number of groups around the country in this regard. Although the topics covered in the present issue are diverse, all have an important clinical context and in this editorial we will attempt to describe this context.

The significance of nitric oxide (NO) in cardiovascular disease, including coronary artery disease, has been recognised for decades. More recently, the role of NO in arterial stiffness[1] and hence systemic hypertension, myocardial remodelling and heart failure[2] has been underscored. From a therapeutic perspective, however, although many drugs (and lifestyle changes) may influence NO, with respect to the development of interventions that specifically target NO, this has only really translated into the use of short- and long-acting nitrates in angina pectoris.[3] In this regard, the development of tolerance or cross-tolerance to nitrates[3] and the exquisite sensitivity of NO production to even small changes in mechanical factors[4] may limit these drug development programmes. Nevertheless, interest in targeting NO production in cardiovascular disease has retained a high profile, including the possibility of gene therapy.[5] In the light of this, it may not be surprising that when requests for basic science contributions to the current edition of SA Heart were forwarded, three separate groups provided papers on the role of NO.

Based on their own and other contributions to this field, on page 174 of this edition Strijdom and Lochner[6] have reviewed the present understanding of the role of myocardial NO on cardiac pathology. Despite the evidence that supports a role for NO in mediating adverse ventricular remodelling[2] and function and dysfunction,[6] the limited capacity of cardiac myocytes to produce NO has forced many of us to take a pragmatic view on the potential that therapeutic targeting of myocardial NO will produce benefits. Strijdom and Lochner have nevertheless provided convincing evidence that cardiac endothelial cells are the dominant source of NO both under normoxic conditions and in hypoxia.[6] Together with recent data to show that a compound that enhances endothelial NO

synthase expression improves function in experimental myocardial infarction,[7] the data provided by Strijdom and Lochner lend credibility to the hypothesis that targeting myocardial as opposed to coronary artery NO production is indeed a worthy pursuit in cardiac pathology. We believe that this will become a 'hot topic' in future drug development.

There is no question as to the importance of hypertension in the generation of cardiac pathology in emerging communities in sub-Saharan Africa.[8] We believe that the poor management of hypertension in these communities represents not only inappropriate care, but also a degree of resistance to drug therapy with many patients requiring multiple agents. Despite the evidence that NO may play a role in blood pressure control - and hence could be a therapeutic target of drug development programmes - unfortunately there is little evidence to support this notion in emerging communities. However, in the present edition of SA Heart, two studies[9,10] provide some evidence to support a role for NO in the pathogenesis of an increased blood pressure in emerging communities.

On page 148 of this edition, Candy, et al.[9] show that in hypertensives off-treatment, the NO synthase gene is associated with an ~7 mm Hg mean difference in ambulatory systolic blood pressure, in a relatively large study for one of this kind (n=503 patients with 24-hour blood pressure data off therapy). This is a remarkable difference considering the impact that this would have on cardiovascular events. These data are even more important considering the recent data from the A-HeFT Trial showing that this genotype is also associated with response to therapy to the isosorbide dinitrate-hydralazine combination in African-Americans with heart failure.[11] Although on more tentative ground, on page 142 of this edition Naidoo, et al.[10] show a positive correlation between concentrations of the precursor for NO, plasma arginine, and ambulatory blood pressure in persons of African descent, arguing that this relationship may represent a reduced capacity for cellular uptake of arginine, a hypothesis that is supported by other authors. Together, these two papers[9,10] suggest that considerably more work is required to evaluate the potential of stimulating NO production or its cellular targets in the treatment of hypertension in emerging communities in Africa.

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As underscored by Vengethasamy, et al.[12] on page 154 of this edition of SA Heart, there is increasing evidence that heart failure may occur in obese patients independent of alternative risk factors and myocardial infarction. This is of considerable importance considering the high percentage of people in emerging communities in South Africa who are obese. However as pointed out by the authors of this paper[12] the mechanisms of obesity-induced myocardial dysfunction are unclear as previous studies have not been able to segregate the adverse effects of blood pressure or diabetes mellitus on the myocardium from those effects produced by obesity per se. In their paper[12] Vengethasamy, et al. provide evidence to suggest that even mild obesity may promote cardiac myocyte apoptosis without increases in blood pressure or diabetes mellitus. This effect was nevertheless only noted in the presence of excessive adrenergic activation and hence these data may be of importance in obese patients with established heart failure where excessive adrenergic activation occurs.

Early myocardial reperfusion is critical to the successful outcome post myocardial infarction.[13] In the South African context however the timing of myocardial reperfusion is far from optimal - hence alternative approaches to reducing myocardial damage incurred by ischaemia/reperfusion are vital. In this regard, there is therefore great interest in identifying the possible molecular mimics of myocardial ischaemic preconditioning (protection by short periods of ischaemia and reperfusion)[13,14] which could be administered either before or during reperfusion to reduce myocardial ischaemia/reperfusion injury.[15] On page 168 of this edition of SA Heart, Somers, et al.[16] provide an important contribution to the expanding literature in this field by excluding the potential role of the classic prosurvival factor Erk in both ischaemic and cytokine (low dose tumour necrosis factor-α) mediated preconditioning. Having excluded Erk, the authors[16] are well placed to identify the key molecular mechanism(s) for drug discovery programmes.

In large clinical studies, it has been shown that levels of apolipoprotein C-III (apoC-III) are a better predictor of risk for coronary artery disease (CAD) than the traditionally measured triglyceride levels.[17,18] Over-expression of apoC-III causes delayed clearance of triglyceride-rich lipoproteins from the plasma resulting in hypertriglyceridemia.[19] In this regard, two promoter region polymorphisms (T-455C and C-482T) in the gene encoding apoC-III may result in increased synthesis of apoC-III and thus contribute to hypertriglyceridaemia.[20] However literature on the possible association between hypertriglyceridaemia and these two apoC-III polymorphisms is inconsistent (cited by Naran, et al.[21]). On page 162 of this edition Naran, et al.[21] provide the first data on these two apoC-III polymorphisms collected in various South African population groups. The study of Naran, et al.[21] suggests that either of these polymorphisms are not associated with increased triglyceride levels in South African populations. Naran, et al.[21] are careful to acknowledge that their study is limited by a small sample size. Possible reasons for the discrepancies in the literature include differences in body mass index (which is a major determinant of triglyceride levels) and the clinical characteristics of the populations studied (presence of CAD, metabolic syndrome or type II diabetes mellitus).

In summary, we are of the belief that this edition of SA Heart showcases just some of the cardiovascular laboratories in South Africa that are engaged in internationally competitive, clinically relevant basic research. We hope that this edition stimulates the much needed further research in these topics and promotes the view that SA Heart represents the interests of an audience who value and engage in both nationally and internationally relevant and competitive research.

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