for 1.1% of male years of life lost and 1.4% of female years of life lost in the same year. This high morbidity and unnecessary mortality occurred despite readily available and cost-effective treatment regimens. The aim of clinical guidelines is to promote good medical practice by assisting practitioners to provide optimal and cost-effective care. Eccles et al. in the former Northern Region of the UK, found that 25% of practices were not aware of the availability of guidelines for the management of asthma, diabetes and hypertension. Studies have found that even when clinical guidelines are available they are not adopted. It is therefore imperative that a strategy promoting the acceptance and use of clinical guidelines by practitioners be developed. By using asthma guidelines, the severity of asthma is more likely to be graded accurately and medicated appropriately. To encourage adherence to the prescribed regimen it is important for practitioners to ensure that patients understand the necessity for and the safety of inhaled steroids. The use of cough mixtures is neither recommended nor indicated in the management of asthma.

The finding in this study that 36.4% of patients did not receive the recommended medication commensurate with the severity of their asthma is cause for concern. If this problem is not addressed, it is unlikely that there will be an improvement in the current unacceptably high morbidity and mortality associated with asthma in South Africa.

Sherwin Kathawaroo
Graham Hukins
Department of Family Medicine
University of the Witwatersrand
Johannesburg


A phosphodiesterase inhibitor promotes the premature development of adverse cardiac remodelling mediated by beta-adrenergic activation in hypertension

To the Editor: Cardiac dilatation is thought to contribute to pump dysfunction in heart failure. In hypertension, left ventricular hypertrophy (LVH) can progress from a concentric geometry to left ventricular (LV) dilatation. The mechanisms responsible for the transition from concentric LVH to cardiac dilatation in hypertension are uncertain. In human studies LVH is associated with an increased sympathetic activity to the myocardium, but not to other tissue beds. Our group has therefore proposed that sympathetic over-activation in LVH could mediate the transition from concentric LVH to cardiac dilatation. Indeed, we have demonstrated that in spontaneously hypertensive rats (SHRs) with concentric LVH, daily administration of low doses of a beta-adrenoreceptor (β-AR) agonist promotes the development of marked cardiac dilatation. However, β-AR-induced effects can be mediated by cyclic adenosine monophosphate (cAMP)-dependent and independent pathways. To explore the role of β-AR-cAMP pathways in mediating the transition from concentric LVH to LV dilatation, we evaluated the effect of a phosphodiesterase inhibitor (PDEI), used either alone or with a β-AR agonist, on LV geometry and function in SHRs with concentric LVH.

Methods

Fourteen-month-old SHRs and Wistar Kyoto (WKY) control rats were used for this study. SHRs either received no therapy, a β-AR agonist (isoproterenol, daily as previously described), a PDEI (pentoxifylline, 50 mg/kg/day in the drinking water), or a β-AR agonist and the PDEI for 3 months. To ensure that the β-AR agonist was effective, additional SHRs were either left untreated or received the β-AR agonist for 5.5 months.

LV cavity size was assessed using three techniques. First, two-dimensional directed M-mode echocardiography was performed using a Sonos model 2500 Hewlett Packard echocardiograph with a 7.5 MHz transducer. Second, LV end diastolic (LVED) dimensions were assessed using piezoelectric ultrasonic transducers placed across the short axis of the heart at controlled LV end diastolic pressures (LVEDP) in open-chest, ventilated rats. Third, LV diastolic pressure-volume relations were constructed in isolated, perfused heart preparations and the volume intercept at a diastolic pressure of 0 mmHg (LV V0) was determined. To assess further the impact of the β-AR agonist and the PDEI on cardiac remodelling, myocardial collagen content was determined using hydroxyproline (HPRO) determinations.
Results

LV cavity dimensions were similar between WKY rats (data not shown) and untreated SHRs (Table I). Although the β-AR agonist was able to induce significant cardiac dilatation after 5.5 months of administration to SHRs (data not shown), 3 months of administration of the β-AR agonist to SHRs failed to induce LV dilatation (Table I). Further, although administration of the PDEI alone failed to modify LV parameters (data not shown), co-administration of the β-AR agonist and the PDEI to SHRs produced marked increases in LV cavity dimensions and myocardial collagen concentrations (Table I).

Discussion

The main findings of this study are that a PDEI potentiates β-AR agonist-mediated LV dilatation in SHRs with concentric LVH. As PDEIs and β-AR agonists share a common cellular pathway, namely the β-AR-cAMP pathway, these data suggest that cAMP is an important mediator of the transition from concentric LVH to LV dilatation. The clinical implication of these findings is that pharmacological agents that increase the activity of this pathway could promote further dilatation in LVH in heart failure.

These findings were presented at the 13th Biennial Congress of the South African Hypertension Society, Johannesburg, 7 - 9 March 2003.

D Badenhorst
C Anamourlis
M Gibbs
M Maseko
O Osadchii
A J Woodiwiss
G R Norton

Cardiovascular Pathophysiology and Genomics Research Unit
Schools of Physiology and Medicine
University of the Witwatersrand
Johannesburg


Table I. Effect of chronic administration of the phosphodiesterase inhibitor (PDEI), pentoxifylline, on left ventricular (LV) dimensions and myocardial collagen characteristics in spontaneously hypertensive rats (SHRs) (mean ± SEM)

<table>
<thead>
<tr>
<th>SHR groups</th>
<th>Placebo</th>
<th>β-AR agonist</th>
<th>PDEI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>Sample size (N)</td>
<td>LVEDD (cm)</td>
<td>LVEDr (cm)</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>0.67 ± 0.02</td>
<td>0.25 ± 0.04</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>0.65 ± 0.03</td>
<td>0.31 ± 0.04</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>0.75 ± 0.03*</td>
<td>0.37 ± 0.03*</td>
</tr>
</tbody>
</table>

*p < 0.05 versus placebo treated.
†At an LVED pressure of 2 mmHg.
β-AR = beta-adrenoceptor; PDEI = phosphodiesterase inhibitor; LVEDD = left ventricular end diastolic diameter; LVEDr = left ventricular end diastolic radius; LV V0 = volume intercept at a left ventricular diastolic pressure of 0 mmHg; HPRO = hydroxyproline.