FACTORS IMPACTING ON LEFT VENTRICULAR HYPERTROPHY IN HAEMODIALYSIS PATIENTS

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of
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DECLARATION

I, James Chabu declare that this thesis is my own work. It is being submitted for the degree of Doctor of Philosophy in the University of the Witwatersrand, Johannesburg. It has not been submitted previously for any degree or examination at this or other University.

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30th day of May, 2008.

I dedicate this work:
To my supportive and understanding wife Adore, my children, Kabanda, Chabu and Lweendo for bearing with my long absence from home
To my mother Mrs. Lucy Musonda Kabanda and to the memory of my late father Mr. Joseph Chabu, who originally inspired me to take up medicine as a career
To God who has been so gracious and kind to me and made it all happen

PUBLICATIONS AND PRESENTATIONS ARISING FROM THIS STUDY

Chabu J, Naicker S, Manga P, Norton G, Olorunju S. Inferior vena cava diameter and collapsibility index in haemodialysis patients correlates with left ventricular geometrical. adaptations. World Congress of Nephrology, April 21-25, 2007. Rio de Janeiro, Brazil. S-P0-0196, page 101, WCN 2007 Book of Abstracts.

ABSTRACT

Left ventricular hypertrophy (LVH) and increases in large artery stiffness predict cardiovascular outcomes in patients with renal failure. What determines left ventricular mass index (LVMI) and large artery stiffness and the contribution toward LVH and large artery dysfunction is not entirely clear. Consequently, this cross sectional study was aimed at assessing the various factors impacting on LVH in haemodialysis (HD), to contribute toward our understanding of the pathophysiology of LVH and large artery dysfunction in 94 adult HD patients. Pre- and post-dialysis blood pressures (BPs) were determined over 12 sessions of dialysis and averaged. Pulse wave analysis performed at the carotid, femoral and radial arteries was employed to determine pulse wave velocity (PWV) and central augmentation index (AIc). Echocardiography was performed to determine left ventricular mass (LVM) indexed to body surface area (LVMI). Natriuretic peptides, procollagen type I c-peptide (PIP), c-terminal telopeptide of type I collagen (ICTP), matrix metalloproteinases and their inhibitors were studied.

The prevalence of LVH was 72.8 % (67/92) .On multivariate analysis pre- ($p \leq 0.005$), post- ($p<0.05$) and averaged dialysis ($p < 0.015$) systolic BP were associated with LVMI and PWV. 24 hour ($r = 0.260$, $p = 0.026$), day ($r = 0.247$, $p = 0.036$), and night ($r= 0.241$, $p = 0.042$) systolic BP were not more closely associated with LVMI than the averaged dialysis systolic BP ($r = 0.272$, $p = 0.010$). Similarly 24 hour ($r = 0.41$, $p = 0.0003$), day ($r=0.400$, $p = 0.0005$), and night ($r =0.416$, $p = 0.0003$) systolic BP were not more closely associated with PWV than the post-dialysis systolic BP ($r=0.39$, $p=0.0001$) indicating that these BP measurements are as effective as 24-hour ambulatory BP in predicting cardiovascular

target organ changes. No relationship between either PWV (r=-0.08), or AIc (r=-0.10) and LVMI, between PWV (r=-0.11), or AIc (r=0.03) and LV MWT was noted. IVCD was independently associated with LVMI (partial r adjusted for average dialysis SBP=0.27, p=0.014; partial r adjusted for 24-hour SBP=0.29, p=0.013), and LV mean wall thickness ($p<0.01$), but not with LV relative wall thickness (p=0.18), or LV end diastolic diameter (p=0.88). An association between IVCD and AIc (partial r adjusted for average dialysis SBP=0.21, $p<0.05$), but not PWV was noted. NT-proANP and NT-proBNP were independently associated with LVMI ($p<0.0001$) but neither were associated with IVCD independent of LVMI suggesting a close association with LVMI in HD. Serum concentrations of matrix metalloproteinases 1, 2 and 9, and their tissue inhibitors (1 and 2) were not associated with LVMI, remodelling or PWV and neither procollagen I nor the C-terminal telopeptide of type I collagen (ICTP) were associated with LVMI. Thus, factors impacting on LVH in this study were systolic BP, NT-proANP, NT-proBNP and IVCD.

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ABBREVIATIONS

BP Ambulatory BP
ABP Ambulatory BP
ACE Angiotensin-converting enzyme inhibitors
ACORD Anaemia correction in Diabetes study
AIc Central augmentation index
AIp Radial augmentation index
ANP Atrial natriuretic peptide
AVA Arterio-venous access
BMI Body mass index
BNP Brain natriuretic peptide
BP Blood pressures
BSA Body surface area
CAD Coronary artery disease
CHF Congestive heart failure
CHOICE Choices for Healthy Outcomes in Caring for ESRD
Ci Collapsibility index
CKD Chronic kidney disease
CRP C-reactive protein concentrations
cSBP Central systolic BP
cSBP Central systolic BP
CV Coefficient of variation
CVD Cardiovascular disease
DBP Diastolic blood pressure
Deceleration time deceleration time of (e)
ECG Electrocardiography
ECM Extracellular collagen matrix
EF Ejection fraction
EIA Enzyme immunoassay
Epoeitin erythropoietin
ESRD End-stage renal disease
Evaluation and Treatment of High Blood Pressure
FS fractional shortening
GFR Glomerular filtration rate
HCU Hand-carried ultrasounds
HD Haemodialysis
Hypertension=1
ICTP C-terminal telopeptide of type I collagen
IHD Ischaemic heart disease
IL Interleukin
ISH Isolated systolic hypertension
IVCD Inferior vena cava diameter
IVCmin Minimum IVC diameter
IVSTd Interventricular wall thickness

JNC VII Seventh Report of the Joint National Committee for the Prevention, Detection,
JVP Jugular venous pressure
K/DOQI Kidney Disease Quality Outcomes Initiative
Kt/V averaged equilibrated urea clearance
Left ventricular dilatation Cavity volume index >90,EF>/+50%
LV MWT Left ventricular mean wall thickness
LVCVI left ventricular cavity volume index
LV-Dilation = left ventricular dilation
LVEDD Left ventricular internal dimensions in end-diastole
Lvesd left ventricular end systolic diameter
LVESD Left ventricular internal dimensions in end-systole
LVH Left ventricular hypertrophy
LVM Left ventricular mass
LVMI Left ventricular mass index
LV-RWT Left ventricular relative wall thickness
LVSD left ventricular systolic dysfunction
MAP Mean arterial pressure
MHD Maintenance haemodialysis
MMP Matrix metalloproteinase
MMP-1Human Matrix Metalloproteinase -1
MMP-2Human Matrix Metalloproteinase -2
MMP-9Human Matrix Metalloproteinase -9
NHLS National Health Laboratory
NT-proANP N-terminal -proanp
NT-proBNP N-terminal fragment of probnp
PDGF Platelet-derived growth factor
PIP Procollagen Type I C-Peptide
PP Pulse pressure
PPc Central pulse pressures
PPp Peripheral pulse pressures
PTH Parathyroid hormone
PVD Peripheral vascular disease
PWV Pulse wave velocity
RAAS Renin angiotensin aldosterone system
RLU Relative light units
RRT Renal replacement therapy
SBP Systolic blood pressure
SBP Systolic BP
TGF Transforming growth factor
TGF-β Transforming growth factor beta)
TIMP Tissue inhibitors of metalloproteinase
TIMP-1Human Tissue inhibitor of Matrix Metalloproteinase 1
TIMP-2Human Tissue inhibitor of Matrix Metalloproteinase 2

PREFACE

The incidence of cardiovascular disease in chronic kidney disease population has been described as reaching epidemic proportions. Cardiovascular mortality in patients on renal replacement therapy is 10–30 times more common than in the general population. Left ventricular hypertrophy (LVH) and large artery dysfunction are prevalent intermediate cardiovascular changes in patients receiving HD. Volume and pressure related risk factors impact LVH and large artery dysfunction. Measurements of circulating natriuretic peptides and their N-terminal pro-hormones and inferior vena cava diameter (IVCD) have been used recently to aid in assessment of appropriate circulating volume. Studies have suggested that changes in collagen I markers, matrix metalloproteinase 1, 2, 9 and their tissue inhibitors (1 and 2) may predict changes in the cardiovascular system. However, what is not entirely clear is exactly what determines these, and the extent to which each factor contributes toward LVH and large artery dysfunction in HD.