

INTRADIALYSIS HYPOTENSION IN PATIENTS WITH
END-STAGE RENAL DISEASE ON CHRONIC
HAEMODIALYSIS AT KENYATTA NATIONAL
HOSPITAL RENAL UNIT.

A dissertation submitted as part fulfillment of the requirements for the
degree of Master of Medicine in internal medicine

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I certify that this dissertation is my own original work and has not been submitted for a degree at any other university.

A handwritten signature in blue ink, appearing to read 'A. Chalopa', with a large initial 'A' and a stylized 'C'.

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List of abbreviations and acronyms

- IDH— Intradialysis hypotension.
- SBP— Systolic blood pressure
- mmHg— millimeters of mercury
- Vs— versus
- KNH—Kenya National Hospital
- LV—left ventricle
- DM—Diabetes Mellitus
- CGN— Chronic Glomerulonephritis
- ESRD— End-Stage Renal Disease
- LVH— Left Ventricular hypertrophy
- Echo— Echocardiogram
- Bp— blood pressure
- f-IDH—frequent intradialysis hypotension
- o-IDH— occasional intradialysis hypotension
- LVDD — Left Ventricular Diastolic diameter
- LVSD — left ventricular systolic diameter
- EF— ejection fraction
- E— early rapid ventricular filling
- A— atrial assisted filling
- ACE-I— Angiotensin-converting enzyme inhibitor
- CCB— Calcium channel blocker
- BB— Beta-blocker
- ARB— Angiotensin receptor-blocker
- Restricti— restrictive

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Abstract

Background: Intradialysis hypotension is a frequent complication in patients with end-stage renal disease on chronic haemodialysis. Problems associated with IDH have a negative impact on health-related quality of life. Morbidity and mortality is high in patients with f-IDH. Factors associated with IDH include: hypovolemia, ventricular dysfunction, autonomic dysfunction, electrolyte imbalance, hypoalbuminaemia, Anaemia and long duration of haemodialysis.

Objective: To study factors associated with the development of IDH in patients with ESRD on chronic haemodialysis.

Design: Descriptive study.

Study population: Patients with ESRD on haemodialysis.

Study Area: KNH renal unit.

Methodology: Files of the 90 patients on haemodialysis at KNH renal unit were scrutinized. Sixty-three with ESRD on chronic haemodialysis were identified and demographic data taken. Cause of ESRD and anti-hypertensive medication in use was ascertained. The number of IDH events in previous three months was noted from dialysis files. Blood was taken from 50 patients who gave consent, for analysis of haemoglobin, albumin, and electrolytes during a dialysis session. Echocardiographic evaluation of LV function was done a day post dialysis.

Data analysis: Data analysis was done using SPSS 11.1 (SPSS Inc. Chicago Illinois USA) statistical package. Comparison of means of continuous variables was made using student t-test, categorical variables using proportions and ratios. Association was determined using chi-square test.

Results: There were 90 patients on haemodialysis during the study period, out of whom, 63(70%) had dialyzed for ≥ 3 months. This group on chronic haemodialysis included 38 males (60.3%) and 25 females. Nineteen (39.7%) of the patients on chronic haemodialysis met the criteria for frequent IDH. Mean age was $46.9 \pm SD 15.8$ yrs for males and $40.6 \pm SD 13.9$ yrs for females. Fifty of the patients on chronic haemodialysis gave consent for inclusion in the study. Diabetes was the cause of ESRD in 30% of the study patients. 88% of the study subjects had hypertension. CCB was the most commonly used anti-hypertension drug (60% of the patients). 66% of the patients had LV diastolic dysfunction. LV diastolic dysfunction was present in 73.7% of the patients with f-IDH and 61.3% of those with occasional or no IDH ($p=0.024$). Mean age of patients with f-IDH and those with occasional or no IDH was 53.2 ± 15.8 & 43.5 ± 14.2 years respectively ($P=0.029$). Patients with f-IDH had low mean serum albumin than those with occasional or no IDH before and after matching for age and sex with a P value of 0.098 and 0.016 respectively.

Conclusion: There was high period prevalence of f-IDH at KNH renal unit. Risk factors for f-IDH in the study population were: Older age, hypoalbuminaemia, diabetes mellitus, and LV diastolic dysfunction.

INTRODUCTION AND LITERATURE REVIEW

Intradialysis hypotension (IDH) is defined as a fall in the systolic blood pressure below 100mmHg accompanied by at least one of the following: diaphoresis, nausea, vomiting, cramps, headache or dizziness, during a dialysis session. When predialysis systolic Bp is <100mmHg, then symptomatic hypotension is defined as a fall in systolic BP of at least 10mmHg accompanied by one of the symptoms listed above ^{1,2}.

The reported incidence of intradialysis hypotension in various studies ranges from 15 – 50% and increases with age ^{2,3,4,5,6}. It contributes to the discomfort experienced by patients during dialysis. Intradialysis hypotension events may lead to long inadequate or discontinued dialysis sessions. There is poor compliance as patients demand for discontinuation of the dialysis session at the onset of any symptoms and this may limit rehabilitation ⁷.

Pathophysiology of hypotension

Ultrafiltration withdraws volume from the haemodynamically active central circulation, where as most of the volume overload resides in interstitial and to a lesser extent, in the intercellular compartment ⁸. There is fluid shift from the interstitial space to the intravascular compartment (refill). Refill is affected by:

- 1) Hydrostatic pressure gradient between capillaries and interstitial space.
- 2) Oncotic pressure gradient between capillaries and interstitial space.

3) Capillary permeability coefficient to plasma proteins.

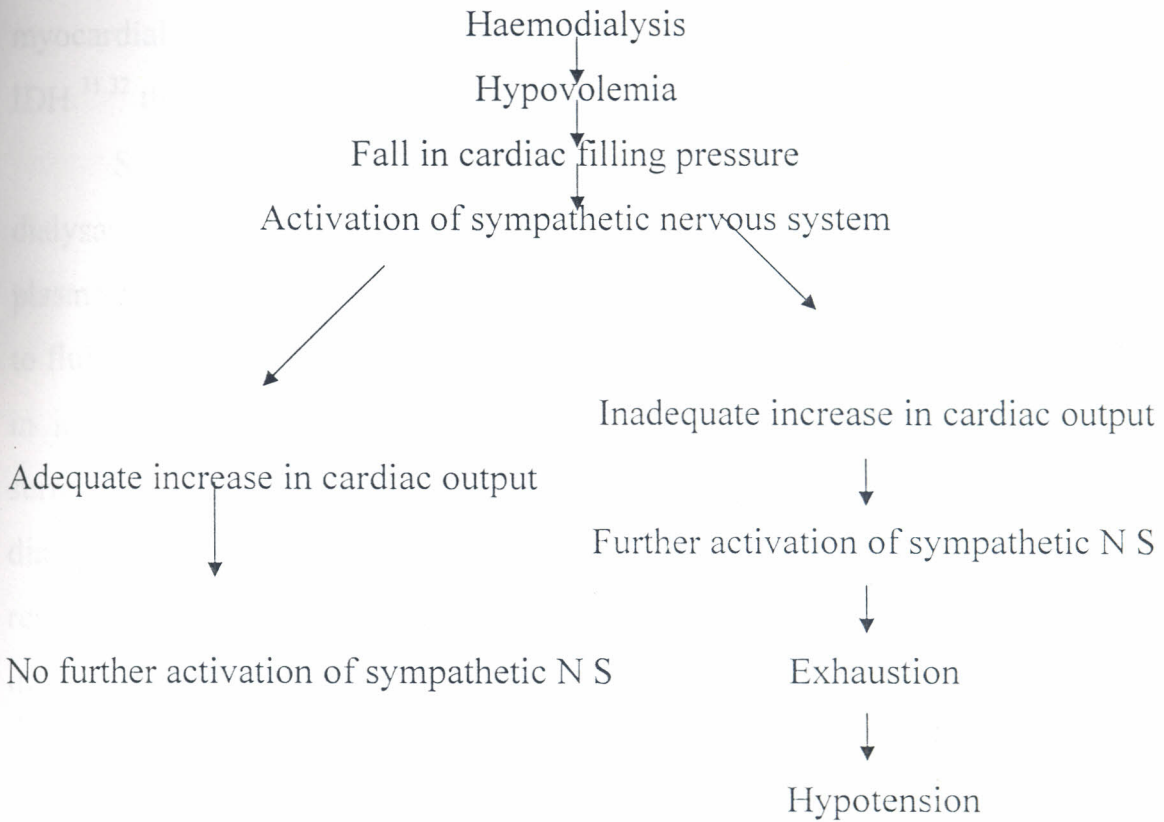
4) Hydrostatic conductivity of capillary walls.

Any changes in the above factors may affect venous return to the heart. Maintaining adequate cardiac filling when venous pressure decreases critically depends on LV diastolic function. Patients with decreased venous pressure and diastolic dysfunction will therefore be prone to IDH because of reduced cardiac output.

Left ventricle hypertrophy is common in end-stage renal disease^{8,9,10}. Anaemia and hypertension that are common features in ESRD contribute a major part to left ventricular hypertrophy. Systolic LV function remains normal in most of these patients despite LVH being present^{11,12}. Concentric LV geometry is very sensitive to abrupt changes of cardiac loading conditions because of increased LV stiffness. LV diastolic dysfunction is due to decreased relaxation¹³. Dialysis-related decrease in LV filling pressure reduces starling forces recruitment and causes a fall in stroke volume¹⁴. There is also myocardial fibrosis in ESRD that contributes to increased LV stiffness and hence diastolic dysfunction. Factors contributing to myocardial fibrosis include angiotensin II, chronically elevated parathyroid hormone, endothelin, aldosterone and increased plasma catecholamines¹³. Ruffman et al¹⁵, found that patients prone to intradialytic hypotension had more significant diastolic dysfunction than a group of stable haemodialysis patients.

Autonomic dysfunction especially in diabetics has been found to play a role in IDH^{16,17,18,19}. This is because of poor compensatory sympathetic response following reduction in intravascular volume.

Scheme of proposed pathophysiological mechanism of haemodialysis-induced hypotension



Don Poldermans et al ²⁰

Differences in pressure response during haemodialysis can be ascribed to difference in the effectiveness of reflex compensatory mechanism ^{21,22,23,24}. Activation of the sympatho-inhibitory cardiodepressor reflex (Bezold-jarisch), which is a physiologic response to a critical reduction in intravascular volume and cardiac filling, is a cause of sudden intradialytic hypotension ^{25,26}. Reduced cardiovascular response to vasopressor agents such as norepinephrine and angiotensin II, associated with down-regulation

of their receptors²⁷, as well as an increased production of vasodilators such as nitric oxide or adrenomedullin are possibly involved²⁸.

Low serum ionized calcium may cause IDH and muscle cramps. Low Ionized calcium decreases cardiac output by decreasing myocardial contractility^{29,30}. High dialysate Calcium improves pressure in IDH^{31,32} though it may also impair cardiac relaxation^{33,34}.

Sodium is a major determinant of effective osmolality in blood and dialysate fluid. When dialysate sodium concentration is lower than that in plasma, the blood returning from the dialyzer will be hypotonic with respect to fluid in the surrounding tissue spaces. This may cause an acute reduction in intravascular volume as fluid moves from intravascular space to the surrounding tissue spaces^{35,36,37}. One may avoid this by using high Na dialysate³⁶ or sodium modeling protocol^{38,39,40}. High sodium dialysate may result in higher intradialytic weight gain due to increased thirst and fluid intake⁴¹.

Food ingestion during haemodialysis has hypotensive effects. Barakat et al⁴² by monitoring thoracic electric bioimpedance in 10 dialysis patients, who ingested a test meal one hour into dialysis, found the hemodynamic mechanism to be a fall in systemic vascular resistance.

Hypoalbuminaemia is a risk factor for IDH. Iseki et al⁴³ followed up 1,243 Okinawan patients on chronic haemodialysis in a prospective study from January 1991 to 1995. BP as well as clinical and laboratory variables were determined immediately prior to the first haemodialysis session in January 1991. Death rate was found to show a significant positive correlation with serum albumin($r=0.135$, $p<0.0001$) and age($r=-0.325$, $p=0.0001$). Diastolic blood pressure showed a significant positive correlation with serum albumin and age.

Morbidity and mortality is high in patients with frequent IDH ^{44,45}.

Tisler et al ⁴⁶ followed up 77 patients with frequent-IDH (≥ 10 hypotensive events/10 months responding only to medical intervention), 101 patients with occasional-IDH (1 or 2 events/10 months) and 85 patients who had no hypotensive episodes for a median of 27 months (range 0.3 – 37). Survival of patients in the three groups was compared by log-rank test. Forty-five patients (58%) with frequent-IDH, 47(47%) with occasional-IDH and 33(39%) with no-IDH died during the follow-up. Mortality rates (death/100 patient years were 37(log-rank $P=0.013$ Vs no-IDH), 26(log-rank $P=0.375$ Vs no-IDH) and 21 in the three groups respectively. This indicates significantly decreased survival in patients with frequent as compared to those with no-IDH. In multivariate proportional hazards regression, however, where age, sex, time spent on dialysis, presence of coronary heart disease, diabetes, Kt/V, albumin level and use of beta blockers, calcium channel blockers and long-acting nitrates has been adjusted for, neither frequent-IDH or occasional-IDH was associated with survival. Foley et al ⁴⁷ observed that low, not high blood pressure was associated with high mortality. Similar findings were also made in other studies ^{48,49}.

Degoulet et al ⁴ in a study of 1110 patients treated with chronic haemodialysis in 32 French dialysis centers, found significant risk factors for symptomatic IDH to be; female sex, diabetic nephropathy as cause of ESRD, two weekly dialysis sessions instead of three, low dialysate osmolarity, low dialysate potassium, high body weight subtraction during sessions, low predialysis plasma proteins, high predialysis blood urea and low nerve conduction velocity.

Tisler et al ⁵⁰ followed up nine hundred and fifty-eight patients at 11 dialysis units for 10 months. Characteristics of patients with frequent

dialysis hypotension ($>$ or $=$ 10 hypotensive events necessitating medical intervention) ($n = 96$) were compared to that of patients with occasional dialysis hypotension (1 or 2 events / 10 months) ($n = 130$). Significant and independent predictors of f-IDH were obtained by multivariate logistic regression. Significant differences between f-IDH Vs occasional dialysis hypotension (oDH) were older age (64.4 Vs 56.9 years, $p < 0.001$), more females (66 Vs 46%, $p < 0.005$) in f-IDH. More f-IDH patients had diabetes (27 Vs 15%, $p < 0.05$) and less had glomerulonephritis 15 Vs 35%, $p < 0.001$) as the cause for ESRD. Coronary artery disease (68 Vs 50%, $p < 0.01$) and long-acting nitrate treatment 51 Vs 30%, $p < 0.001$) was more frequent while treatment ACE-I (33 Vs 48%, $p < 0.05$) or Ca-channel blockers (40 Vs 53%, $p < 0.05$) were less frequent in patients with f-IDH. Patients with f-IDH had higher serum phosphorous levels 1.99 Vs 1.79 mmol, $p < 0.005$).

Ning et al ¹⁶ in a study of 25 diabetic mellitus (DM) and 40 chronic glomerulonephritis (CGN) patients on haemodialysis found, autonomic dysfunction in 80% of DM and 57.5%, $P < 0.05$ of CGN patients. During haemodialysis, hypotension rate was 37.2% in those who had autonomic dysfunction and 18.2%, $P < 0.05$ in those with normal autonomic nerve function.

IDH has multiple pathogenic causes and this explains why therapies that modulate only a specific aspect of the problem are only partially effective. Interdialysis weight gain that is mainly used to assess amount of ultrafiltrate is not adequate. Simultaneous increase of post-dialysis body weight and decrease of pre-dialysis mean arterial blood pressure may be related to anabolism induced by haemodialysis and normalization of blood pressure by fluid removal. Continuous clinical assessment of patients is

necessary to provide adequate prescription of post-dialysis body-weight ⁵¹. One should have predialysis minimal data set to be able to identify patients with high risk for IDH. The high risk ones should have ultrafiltration kept within a safe margin (UF= \leq 3% of body weight) ⁵².

Lower ultrafiltration rate may be required for high-risk patients ^{53,54}. Eric et al ⁵⁵ demonstrated the need for echocardiographic evaluation of LV diastolic function being done postdialysis and not predialysis. Predialysis hypervolaemia has masking effect on impairment of early LV diastolic filling resulting in pseudonormalization of transmitral blood flow pattern.

Study justification

Intradialysis hypotension occurs in 15—50% of patients on chronic haemodialysis. It leads to prolongation or discontinuation of dialysis session and hence poor quality of haemodialysis. Management of intradialysis hypotension (IDH) consumes a lot of staff time and financial resources. A lot of time is spent resuscitating patients during IDH events thus straining limited staff in such specialized unit and denying other patients adequate attention. When a dialysis session is discontinued after say two hours instead of scheduled six hours because of hypotension, it requires that the patient gets more sessions per week than the usual two at the KNH renal unit. Each session requires new provisions that have to be bought by the patient hence increasing the cost. IDH has been associated with high morbidity and mortality in patients with ESRD on chronic haemodialysis.

There is no literature on the condition in Africa. Anecdotal observations at KNH renal unit had shown a significant number of patients have hypotension during dialysis. The study therefore aimed at filling this knowledge gap.

It is hoped that modification of risk factors for f-IDH identified in this study will help improve the quality of life and hopefully reduce the high morbidity associated with the condition.

Broad objective:

To study factors associated with the development of intradialysis hypotension in patients with ESRD on chronic haemodialysis at Kenyatta National Hospital renal unit.

Specific objectives:

- 1) To determine the period prevalence of frequent intradialysis hypotension in chronic haemodialysis patients at Kenyatta national hospital.
- 2) To determine serum Calcium, potassium, sodium, inorganic phosphorous, albumin, haemoglobin level in patients with frequent intradialysis hypotensive events and those with occasional or no IDH.
- 3) Assess left ventricular function in patients with frequent intradialysis hypotension and those with occasional or no IDH.
- 4) To document the Cause of ESRD in patients with frequent IDH and those with occasional or no IDH.
- 5) To document the antihypertensive medications in use in patients with frequent IDH and those with occasional or no IDH.
- 6) To compare Ca, K, Na, inorganic phosphorous, albumin, haemoglobin, and echocardiographic findings between patients with frequent IDH and those with occasional or no IDH before and after matching them for age and sex.

METHODOLOGY

Study area: KNH Renal Unit.

Study population: All patients with ESRD undergoing chronic haemodialysis in the renal unit during the study period were recruited.

Sampling method: This was a population study of all patients on chronic haemodialysis.

Study design: Descriptive study.

Inclusion criteria:

Patient with ESRD on haemodialysis for three or more months.

Age over 18 years.

Informed consent.

Exclusion criteria:

Denied consent.

Recruitment.

Files of all dialysis patients at KNH renal unit were perused to identify those with ESRD on chronic haemodialysis. A patient was considered to be on chronic haemodialysis if he/she had been on dialysis for three or more months. A thorough scrutiny of case and dialysis files of patients with ESRD on chronic haemodialysis was made.

Data collection:

Demographic data was extracted for all patients with ESRD on haemodialysis. Age, sex, duration of haemodialysis, the antihypertensive medications in use and the time of diagnosis, was noted, (**appendix IV**). History of diabetes and duration of disease before the diagnosis of ESRD was established from clinical interview and patients' records. The cause of ESRD was documented from the files. Each patient on haemodialysis at KNH renal unit has a well-kept dialysis file in which charts of vital signs, complaints and any interventions during a dialysis session are recorded. The Bp is usually taken with the patient supine in the dialysis bed.

The number of intradialysis hypotension events in the previous 3month was established from the dialysis files, **appendix IV**.

Definition of intradialysis hypotensive event

- a) A symptomatic decrease in systolic BP by at least 25mm Hg with respect to pre-dialytic value and the need for therapeutic intervention (Trendelenburg, intravenous fluid infusion, or termination of the session).
- b) A symptomatic reduction in systolic blood pressure < 100mm Hg.

- c) A symptomatic decrease in systolic blood pressure by at least 10% in chronically hypotensive patients starting the dialysis session with a systolic blood pressure lower than 100mm Hg.

Using the above, we identified two groups of patients among those on chronic haemodialysis:

Group A: Patients with frequent IDH. These were patients who had had three or more events of symptomatic hypotension in the previous three months.

Group B: Patients with occasional or no IDH events. These were patients who had had less than three or no IDH events in the previous three months.

All patients with end-stage renal disease on chronic haemodialysis who gave consent were recruited. Blood was drawn from all the patients mid-way through a dialysis session for laboratory analysis. This was for the purpose of standardization. Each patient recruited was only investigated once during the study period.

A venous sample of 5mls of blood drawn in a heparinized syringe was taken to the renal laboratory for determination of haemoglobin level, albumin, and serum calcium, potassium, sodium and inorganic phosphorous. Patients were given an appointment for echocardiographic evaluation a day post the dialysis session.

Laboratory analysis methods.

Biochemistry:

Serum Calcium ion assay: RANDOX colorimetric method. Principle: Ca ions form a violet complex with O-cresolphthalein complexon in an alkaline medium.

Inorganic Phosphorous assay: RANDOX colorimetric method. Principle: inorganic phosphorous reacts with ammonium molybdate in the presence of

sulphuric acid to form a phosphomolybdate complex which is measured at 340nm.

Serum Sodium and Potassium ions assay: Electrode method using 654 Na+/K+/Li Analyzer ⁵⁶.

Albumin: Analyzed using Technicon RA® systems ⁵⁷. Serum sample is added to bromcresol green (BCG) reagent to form albumin-BCG complex the analytical solution is mixed for approximately 30 seconds and the absorbance is measured at 600nm.

Echocardiogram: The investigator assisted by two experienced echocardiography technologists, undertook echocardiogram of LV function assessment, a day after a haemodialysis session. A General Electric 2-D & Colour Doppler was used. Standard Echocardiography of LV function was done, using both M mode and 2-D imaging. Left ventricular end-diastolic diameter (LVDd), left ventricular end-systolic diameter (LVSD) and left ventricular ejection fraction (EF) were taken to assess LV systolic function. E/A ratio before and after Valsalva manoeuvre, were used in assessing LV diastolic function. Having patients maintain intra-thoracic pressures of 60cm of water using a manometer was used to standardise the Valsalva manoeuvre procedures.

Data handling and analysis

Data were collected using the proforma. It was then entered into a computer using the SPSS 11.1 statistical package. The data were then verified and cleaned. Demographic data gathered from the files and interview of all patients on chronic haemodialysis in the renal unit, **appendix IV**, were used in the study to determine:

- 1) Prevalence of intradialysis hypotension in chronic haemodialysis patients in the renal unit.
- 2) The cause of ESRD in chronic haemodialysis patients. The cause of ESRD was grouped as either diabetic or non-diabetic related.
- 3) Antihypertensive medications in use in chronic haemodialysis patients. The antihypertensive drugs were categorized as calcium channel blockers, ACE inhibitors, centrally acting drugs, beta-blockers and angiotensin-receptor blockers.

The data was summarized into means, median, proportions and standard deviations. Results are presented in form of tables, pie charts, bar charts and histograms. Comparison of sample means of serum calcium, potassium, sodium, phosphate, albumin, and haemoglobin level were done using Student t-test. Comparison of age, sex, cause of ESRD, medication in use and LV diastolic function, was done using proportions and ratios. Chi-square tests of significance are used to determine association. Statistical significance is defined as a two-tailed p value of less than or equal to 0.05.

Ethical consideration

Approval and permission to carry out this study was sought from the department of medicine of the faculty of medicine, University Nairobi, the ethical and research committee of KNH. Benefits of the study were fully explained to the patients, so were the expected risks. Informed consent was given in writing or by fingerprinting. Patients' data were treated with utmost confidentiality at all stages of the study. Only samples intended for the study were drawn. Results relevant to the management of the patient were promptly relayed to the renal physician on call. Results will be published and a copy put in the medical library to provide a source of information for future research. Renal Unit staff will have access to the results of the study.

RESULTS

The study was carried out from October to November 2004. A total of ninety patients were on haemodialysis in KNH renal unit during that period. Thirty-six (40%) of these patients were females, while the rest, 54 were males. The mean age of the patients was $44.4 \pm \text{SD } 15.3$ years, with a range of 15 to 77 years (figure I). The mean age for males was 46.9 ± 15.8 years while females it was 40.6 ± 13.9 years. The difference in age was not statistically significant at a p value of 0.058. There are two peaks in age distribution of patients with ESRD disease on chronic haemodialysis, at 30 years and at 55 years.

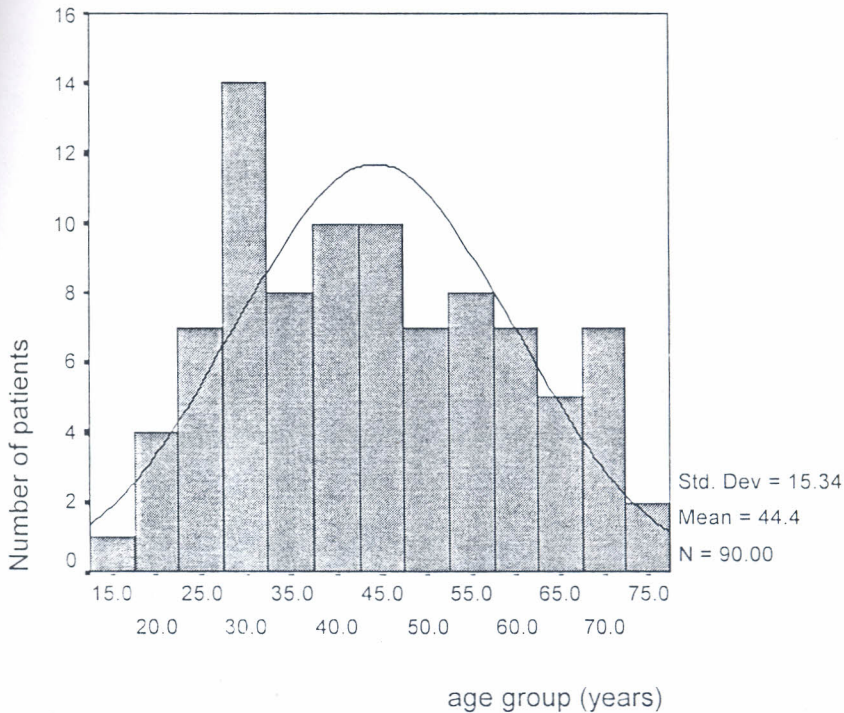


Figure I: Age distribution of all haemodialysis patients.

Out of the 90 patients on dialysis at the KNH renal unit, 63 (70%) had been on haemodialysis for three or more months (chronic haemodialysis) and hence qualified for inclusion into the study. Twenty-seven (30%) of the patients had dialyzed for less than three months and were therefore excluded from the study. Thirty-eight (60.3%) of the patients on chronic haemodialysis had less than three or no intradialysis hypotensive events (occasional or no IDH) in the previous three months.

Twenty-five (39.7%) of the patients on chronic haemodialysis had 3 or more IDH events (f-IDH) in the previous 3month. This gives a period prevalence of f-IDH in patients on chronic haemodialysis at KNH renal unit of 39.7%. The 63 patients on chronic haemodialysis included 38 (60.3%) males and 25 females. The mean age was, males $49.5 \pm \text{SD } 16$ years and females $42.1 \pm \text{SD } 14$ years, with no statistical significant difference at a p value of 0.062.

Thirteen out of the 63 (20.6%) patients who qualified for inclusion into the study were excluded. Flow of patients through the study is shown below (figure II).

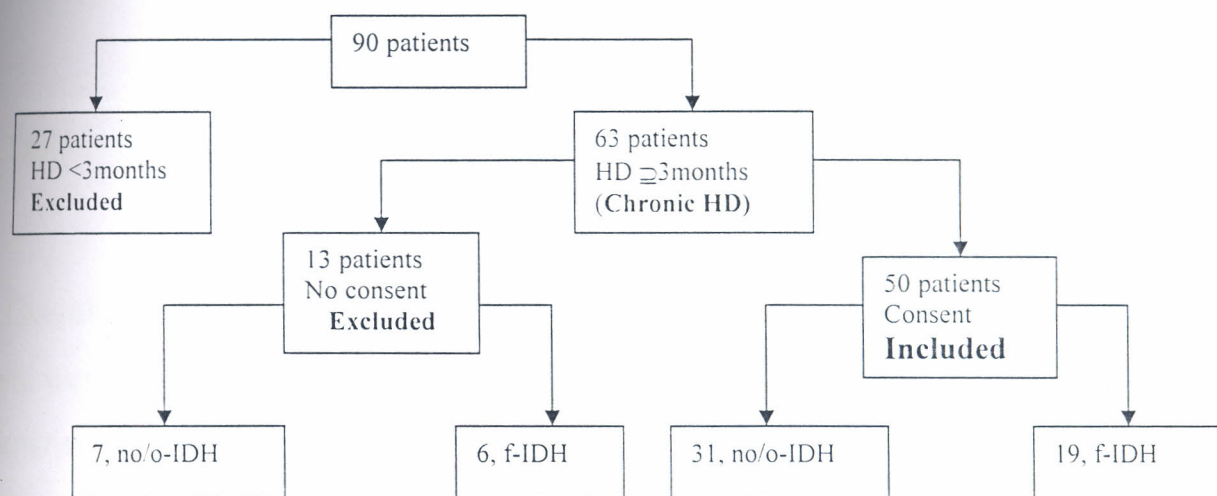


Figure II: Haemodialysis Patients at KNH renal unit

The 13 patients were excluded for various reasons, namely,

1. One patient left for renal transplant before echocardiography was done.
2. Three patients who all had frequent IDH events died before investigations were done.
3. Nine patients either gave no consent or did not avail themselves for the study after giving consent.

They included six females (46%) and seven males. They ranged in age from 27 to 77 years, with a mean age of $44.5 \pm \text{SD } 16$ years. Characteristics of the excluded patients are summarized in table I. There was no selection bias as the percentage of patients with, diabetes as the cause of ESRD, f-IDH and gender distribution was similar in both excluded and included populations.

	Number	Percentage
Female	6	46
Diabetic	3	23
Hypertension	2	15.4
f-IDH	6	46
Mean age (yrs)	44.5±16	

Table 1: Characteristics of the 13 patients excluded after initially qualifying for the study.

Overall, only 50 patients out the 63 on chronic haemodialysis gave consent and were included in the study. They included 31 (62%) males and 19 (38%) females. This is fairly representative of all patients on haemodialysis where 40% were females.

The fifty study subjects had a wide age range of 18 to 75 years with a mean of $47.18 \pm \text{SD } 15.39$ years, (figure III). The age range and mean age is similar to that of the whole population on haemodialysis in the renal unit. There are three peaks at age of 30, 55 and 70 years.

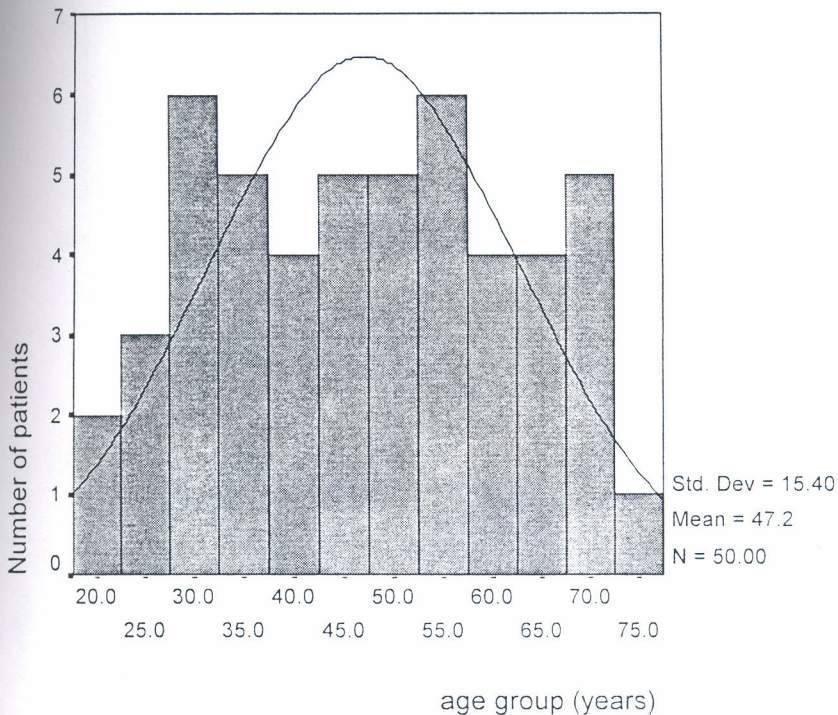


Figure III: Age distribution of the 50 study subjects.

The mean age for males was $49.6 \pm \text{SD } 15.6$ years and females $43.2 \pm \text{SD } 14.6$ years, there being no statistical significant difference at a p value of 0.151.

Most of the patients on chronic haemodialysis had dialyzed for less than 3 years, with only one patient having dialyzed for over 10 years. The mean duration of haemodialysis was $2.30 \pm$ SD 2.57 years, with a range of 0.42 to 16 years, (figure IV).

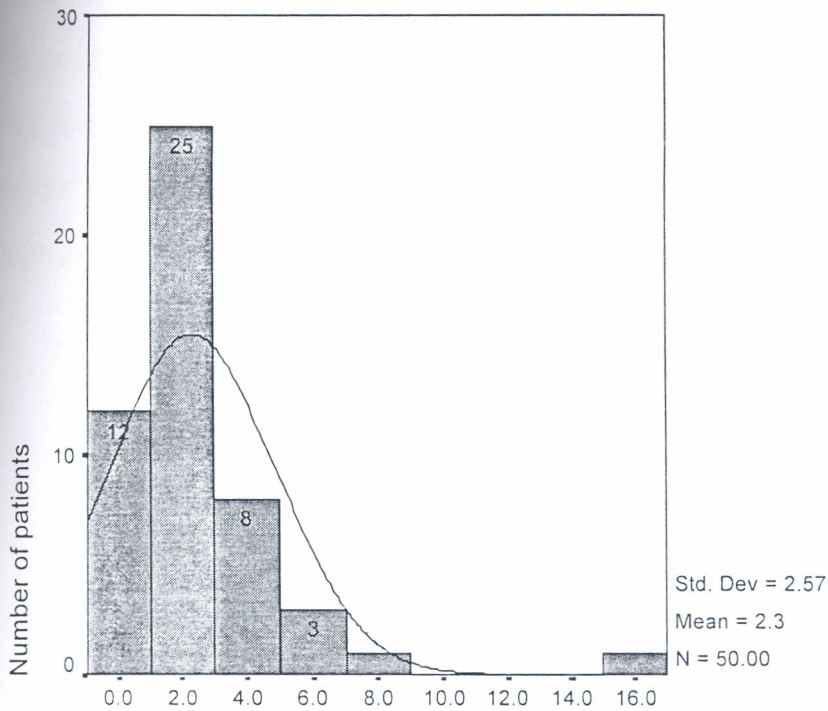


Figure IV: Duration of haemodialysis (yrs) for the 50 study subjects.

The aetiology of ESRD in 15(30%) of the study patients was diabetes mellitus. In 35 (70%) of the patients the cause of ESRD was non-diabetic related though we could not establish exactly what it was from this study.

Forty-two (88%) of the study subjects had hypertension and were on anti-hypertensive drugs.

The most commonly prescribed anti-hypertensives were: calcium channel blocker (CCB) 60%, beta-blocker (BB) 46%, and angiotensin-converting enzyme inhibitor (ACE-I) 34%, either as single drug or in combination, and others as shown in figure V.

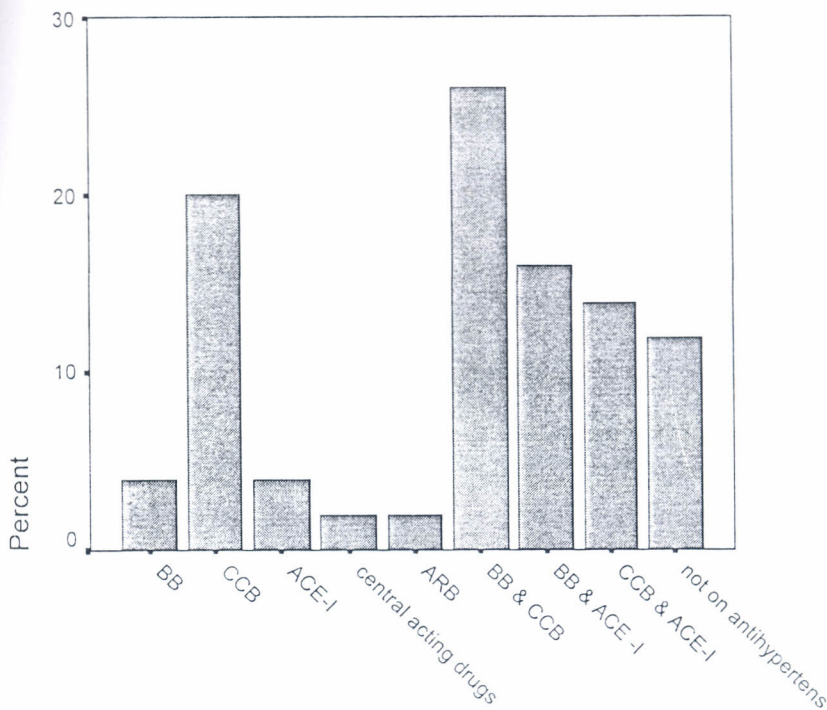
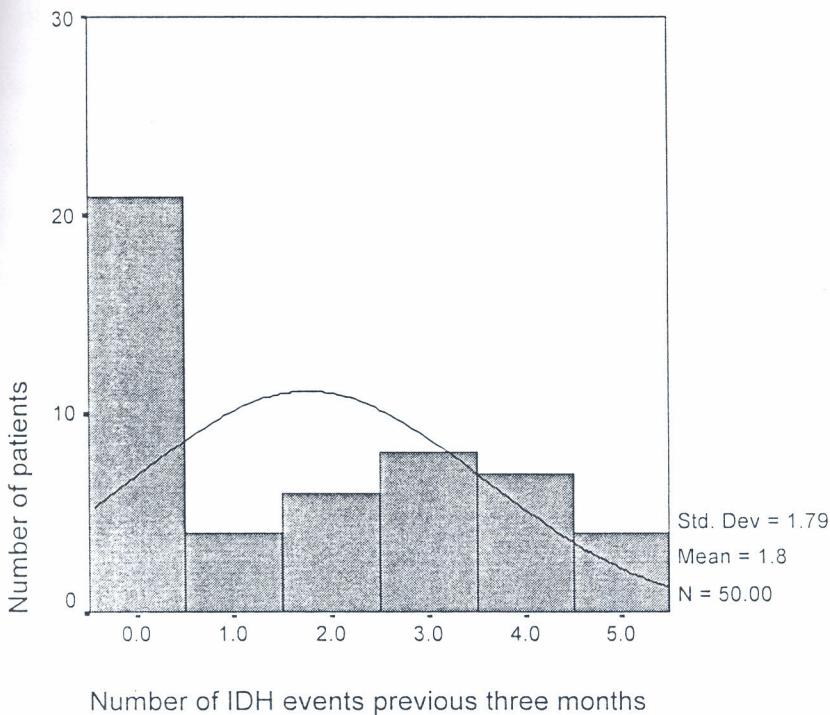


Figure V: Anti-hypertensives use in the study subjects.

Twenty-two of the patients had no IDH in the previous three months. The other 38 had IDH events ranging from one to five. Nineteen (38%) of the 50 study subjects were found to have frequent IDH.

Thirty-one patients (62%) were found to have occasional or no IDH events (figure VI). This compares with the 39.7% patients with f-IDH out of the 63 on chronic haemodialysis. Therefore despite some patients giving no consent and being excluded, the study group is well representative.



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Figure VI: Intradialysis hypotension events in the previous three months.

Most study subjects had hypocalcaemia and hyperphosphataemia with a mean of $2.06 \pm \text{SD } 0.33$ mmol/L and $2.38 \pm \text{SD } 0.72$ mmol/L respectively.

Mean serum potassium was $5.35 \pm \text{SD } 0.67$ mmol/L while for sodium it was $136.94 \pm \text{SD } 6.11$ mmol/L. Anaemia was prevalent in the study subjects with a mean haemoglobin of $8.55 \pm \text{SD } 1.35$ g/dL. The mean serum albumin for 50 patients was $38.15 \pm \text{SD } 4.52$ g/L.

The 2-D echocardiogram was done on the 50 study subjects to assess LV diastolic function. Seventeen (34%) of the study subjects had normal LV diastolic function. Majority, (66%) had LV diastolic dysfunction in various stages as follows; stage I, impaired relaxation, 36%, stage II, pseudonormalisation, 10%, stage III, reversible restrictive, 4% and stage IV, fixed restrictive, 16% (figure VII).

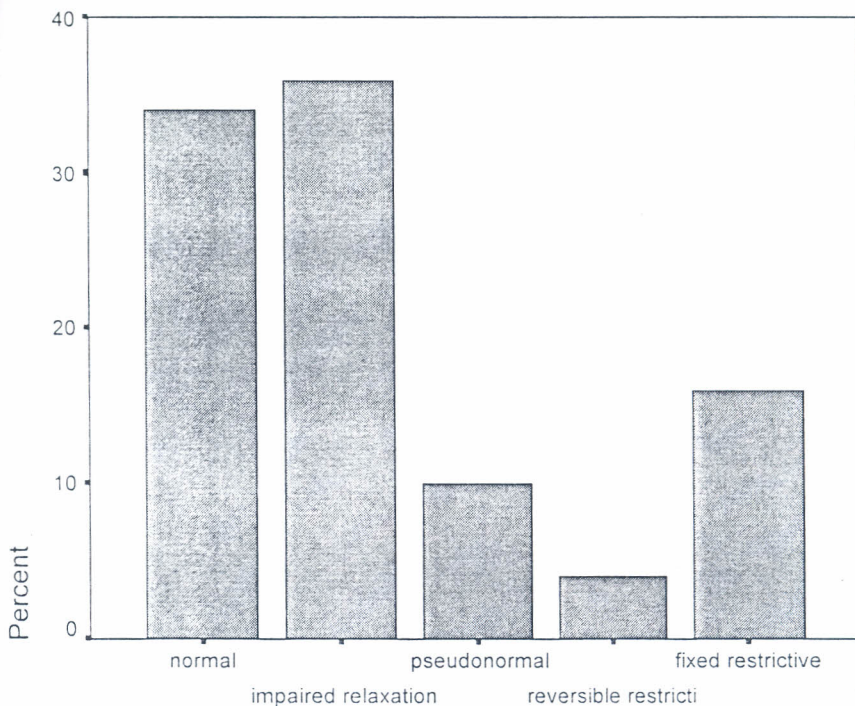


Figure VII: Left ventricular diastolic function.

Out of the 31 males in the study group, 13 (41.9%) had frequent IDH. The females with f-IDH were six out of the total of 19 (31.6%), (figure VIII). Overall as seen earlier, 38% of the 50 study subjects had f-IDH. The difference was statistically insignificant at a p value of 0.468.

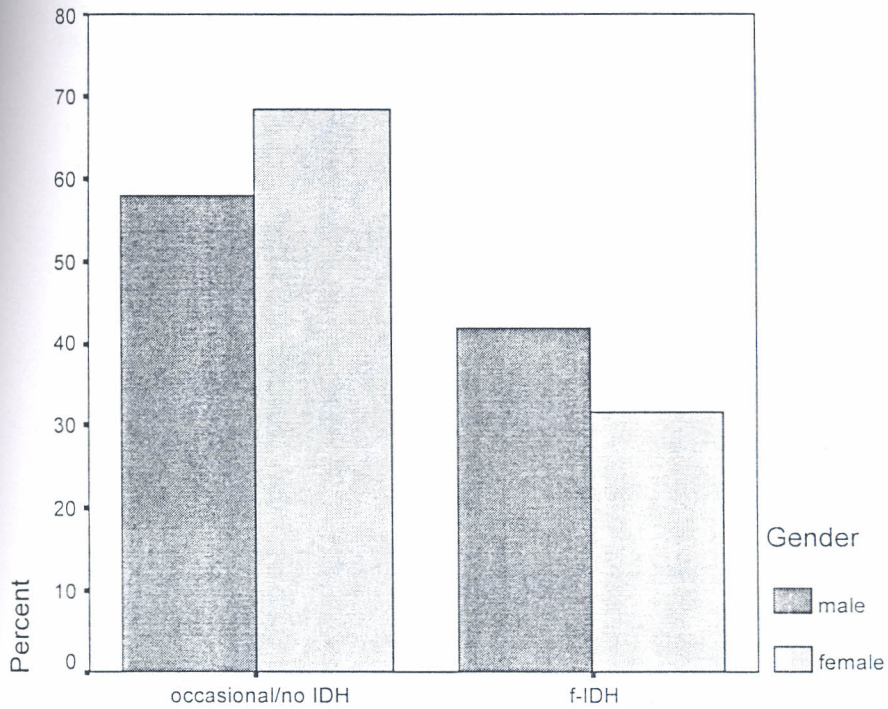


Figure VIII: IDH events and gender in the 50 study subjects.

Fourteen out of the 19 (73.7%) patients with frequent IDH had LV diastolic dysfunction. LV diastolic dysfunction was present in 19 out of the 31 (61.3%) patients with occasional or no IDH event, (figure IX). The difference in LV diastolic function between the two groups was statistically significant at a p value of 0.024.

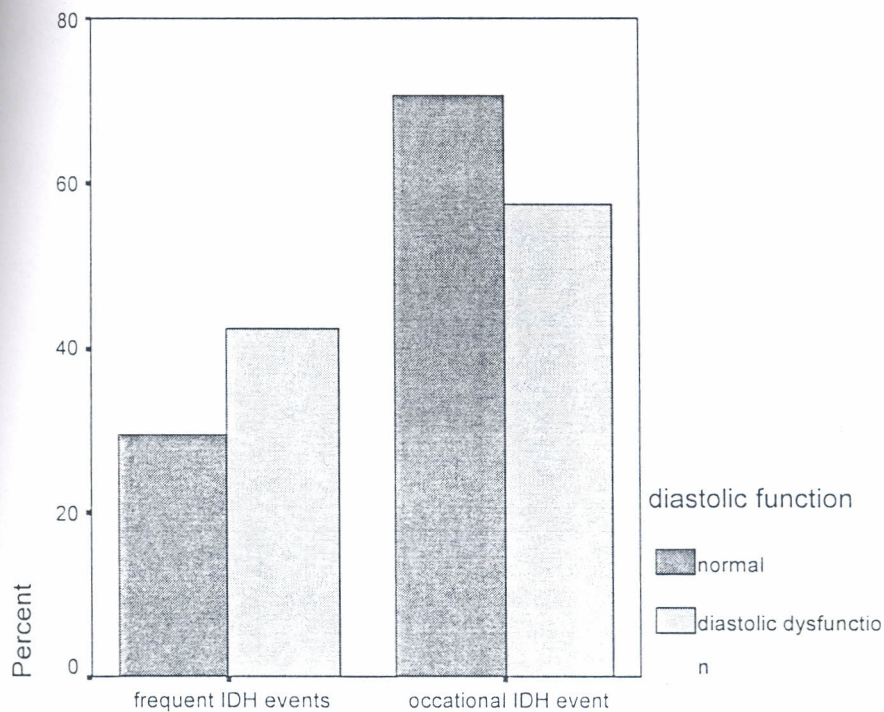


Figure IX: LV diastolic function and IDH events.

Anti-hypertensive drugs use was compared between patients with f-IDH and those with occasional or no IDH to find out if the choice of drugs had any influence on IDH events (figure X). The most commonly prescribed anti-hypertensive drugs in patients with occasional or no IDH event was a combination of a calcium channel blocker and beta-blocker (22%), and a combination of CCB & ACE-I (10%). CCB alone and a combination of BB & ACE-I were associated with f-IDH. Taken overall, 52.6% of the patients with f-IDH and 64.5% of those with occasional or no IDH, were on CCB alone or in combination with other drugs.

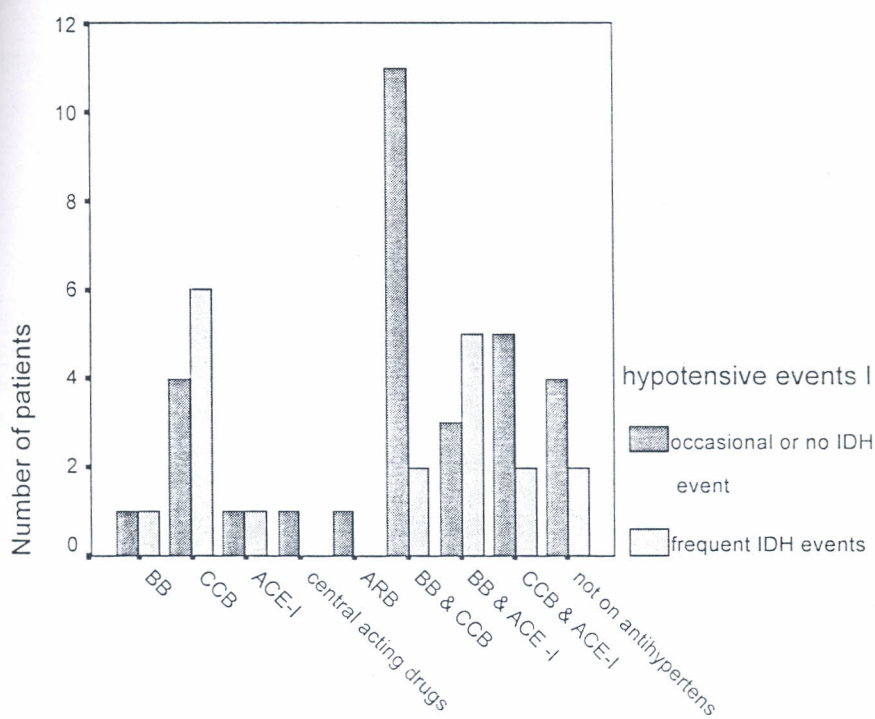


Figure X: Anti-hypertensives use in patients with frequent and those with occasional or no IDH events.

The aetiology of ESRD in patients with f-IDH and in those with occasional or no IDH was diabetes mellitus in 36.8% and 25.8% respectively with a statistically significant difference at a p value of 0.05. The mean age of patients with f-IDH was 53.21± SD 15.78 years while that of patients with occasional or no IDH was 43.48± SD14.16 years. The age difference was statistically significant at a p value of 0.029.

The mean duration of haemodialysis were 1.57±SD 1.07 years for the patients with f-IDH and 2.75±SD 3.09 years for those with occasional or no IDH, the difference was statistically insignificant at a p value of 0.114.

The demographic characteristics of patients with frequent IDH were compared with those of patients with occasional or no IDH (table 2).

	Frequent-IDH 19pts (38%)	Occasional-IDH 31pts (62%)	t-test Sig. (2-tailed)
Number of males 31	13 (68.4%)	18 (58.1%)	P=0.468
Number of females 19	6 (31.6%)	13 (41.9%)	P=0.468
Diabetic patients	7(36.8%)	8(25.8%)	P=0.05
Mean age yrs.47.18±15.40	53.21±15.78	43.48±14.16	0.029
Duration of HD in years.2.30±2.57	1.57±1.07	2.75±3.09	0.114

Table 2: Comparison of demographic characteristics and duration of HD of the 50 study subjects.

The mean, serum calcium, potassium, sodium, phosphate, and albumin and LV ejection fraction of patients with frequent IDH was compared to that of patients with occasional or no IDH (Table 3).

The difference between the two groups was statistically insignificant for all the above outcome measures.

	Frequent-IDH 19 patients	Occasional-IDH 31 patients	t-test Sig. (2-tailed)
Mean Calcium (mmol/L). 2.06±0.33	1.97±0.30	2.11±0.34	0.213
Mean potassium (mmol/L). 5.35±0.67	5.55±0.8	5.22±0.57	0.101
Mean sodium (mmol/L). 136.94±6.11	136.32±7.06	137.32±5.55	0.577
Mean phosphate (mmol/L). 2.38±0.72	2.42±0.75	2.36±0.72	0.791
Mean haemoglobin (g/dL). 8.55±1.35	8.46±1.29	8.60±1.4	0.726
Albumin (g/L). 38.15±4.52	36.80±4.82	38.98±4.1	0.098
LV ejection fraction. 62.57±16.80	61.47±17.73	63.24±16.46	0.721
LV diastolic dysfunction	14 (73.7%)	19 (61.3%)	P=0.024
Beta-blocker	8 (42.1%)	15 (48.4%)	P=0.152
CCB	10 (52.6%)	20 (64.5%)	P=0.832
ACE-I	8 (42.1%)	9 (29.0%)	P=0.018

Table 3: Outcome measures in the 50 study subjects.

Part two:

Fifteen patients with frequent IDH were matched for sex and age to the nearest five years to those with occasional IDH.

Four patients with frequent IDH could not be matched and were excluded from this part of analysis. The patients who could not be matched were over 60 years of age.

Comparison of serum Ca, K, Na, inorganic phosphorous, albumin, haemoglobin, and LV diastolic function was made between patients with frequent and those with occasional or no IDH events (table 4). Albumin level was the only variable found to be significantly different for the two groups. There were more patients on calcium channel blockers and/or ACE-inhibitor in the occasional or no IDH group than in the frequent-IDH group.

	Frequent-IDH 15 Pts	Occasional-IDH 15 Pts	t-test Sig. (2-tailed)
Diabetic	5(33.3%)	5(33.3%)	
Non-diabetic	10(66.7%)	10(66.7%)	
Mean age yrs.	48.53±14.37	48.13±15.23	
Duration of HD. 2.23±2.91	1.64±1.18	2.81±3.9	0.277
Mean Calcium (mmol/L). 2.00±0.26	1.96±0.26	2.04±0.27	0.436
Mean potassium (mmol/L). 5.31±0.73	5.49±0.87	5.14±0.53	0.198
Mean sodium (mmol/L). 137.10±6.85	136.93±7.10	137.27±6.84	0.897
Mean phosphate (mmol/L). 2.40±0.76	2.48±0.81	2.33±0.68	0.574
Mean haemoglobin (g/dL). 8.24±1.29	8.25±1.36	8.23±1.26	0.967
Albumin (g/L). 37.44±4.75	35.41±3.88	39.47±4.78	0.016
LV ejection fraction. 62.74±15.91	62.67±17.35	62.81±14.9	0.981
Normal LV diastolic function	4(26.67%)	7(46.67%)	
LV Diastolic dysfunction	11(73.33%)	8(53.33%)	P=0.079
On a CCB	7(46.67%)	10(66.67%)	P=0.465
On a beta-blocker	6(40%)	6(40%)	
On an ACE-Inhibitor	5(33.33%)	7(46.67%)	P=0.273

Table 4: Comparison of the outcome measures between patients with frequent and those with occasional or no IDH events.

Higher number of patients with frequent IDH events had LV diastolic dysfunction (73.33%) as compared to those with occasional or no IDH event (53.33%), after matching them for age and sex, (figure XI), though the difference was not statistically significant, (P=0.079).

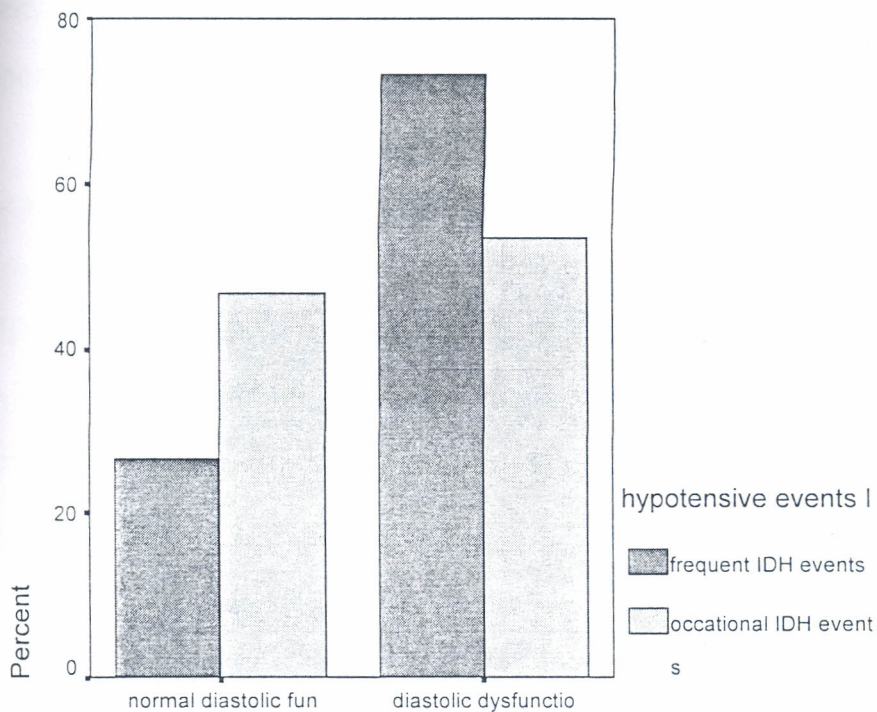


Figure XI: LV diastolic function in patients matched for age and sex.

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DISCUSSION

This is one of the first studies on the prevalence of frequent intradialysis hypotension in patients on chronic haemodialysis to be done in Africa. The study found a very high period prevalence of f-IDH of 39.7% at Kenyatta National Hospital renal unit. In studies done elsewhere, IDH is reported to occur in 15-50% of the patients on haemodialysis^{2,3,4,5,6}.

Majority of the patients (60.3%) on renal replacement therapy with haemodialysis were males. This would raise a question; is there more chronic renal disease among males or is there other reason to explain the big difference? Economic difference could be part of the reason. Females are generally less financially able and hence a lot of them may not be accessing dialysis services. In this study females contributed to 31.6% of the 19 patients with frequent IDH and 41.9% of the 31 with occasional or no IDH events, with an insignificant statistical difference ($P=0.468$). This differs from what has been reported in other studies^{4, 46, 50}, where it has been found that female gender is a risk factor for f-IDH. Tisler et al⁵⁰ looked at 96 patients with f-IDH and 130 with no IDH, females were 66% and 46% of the two groups respectively, with a statistically significant difference at a P value of <0.005 .

The mean age of patients on chronic haemodialysis was 46.6 ± 15.4 years with a range of 18 years to 77 years. This is a younger population than that of patients with chronic renal insufficiency (52.7 years) at KNH medical out patient clinics studied by Sheikh⁵⁸. In our study the males were older than females, with mean ages of 49.6 and 43.2 years respectively. The mean age of patients with frequent IDH (53.21 ± 15.78 yrs) was higher than that of patients with occasional or no IDH events (43.48 ± 14.16 yrs), with a

significant P value of 0.029. Akocsi et al ⁵⁰ found similar age related differences with a P value of <0.001. The population studied by Akocsi et al ⁵⁰ was older with mean age of 64.4 years for patients with f-IDH and 56.9 years for those with occasional IDH. The above findings are expected, given that LV diastolic dysfunction, a risk factor for f-IDH ¹⁵, increases with age from 50 years. One has to anticipate IDH in the older patients, and therefore monitor them more closely.

Diabetes mellitus was the cause of ESRD in 30% of the patients on chronic haemodialysis. These compares with figure of 28.9% found by Sheikh ⁵⁸ when he looked at 83 patients with chronic renal insufficiency at KNH. Among the 19 patients with frequent IDH, diabetes mellitus was the cause of ESRD in 7 (36.8%) of them. The figure was 8(25.8%) of the 31 patients with occasional or no IDH events, P value 0.05. This implies that diabetes mellitus, as a cause of ESRD is a risk factor for f-IDH. Tisler et al ⁴⁰ in a study in which he looked at 96 patients with f-IDH and 130 with no IDH events found 27% and 15% to be diabetics respectively, with a significant P value of <0.05. Degoulet et al ⁴ also found similar results. Diabetes is closely related with hypertension, cardiovascular disease and LV hypertrophy, which lead to LV diastolic dysfunction.

Autonomic dysfunction is a complication of long standing diabetes as well as ESRD. Amayo et al ⁵⁹ found autonomic neuropathy in 68% of the 22 patients they studied with chronic renal failure at KNH on conservative management in 1994. Though autonomic neuropathy was not looked for in this study, its one of the causes of intradialysis hypotension ^{16,17,18,19}. Ning et al ¹⁶ was able to demonstrate high percent of autonomic neuropathy during haemodialysis in patients with diabetes as a cause of ESRD as compared to those with chronic glomerulonephritis. Autonomic neuropathy predisposes

one to IDH by interfering with compensatory sympathetic mechanisms that come into play following volume reduction during dialysis.

Twenty-six percent of the study patients were on a combination of a beta-blocker and a calcium channel blocker for treatment of hypertension, while 20% were on a calcium channel blocker alone. Use of ACE-I was a significant risk factor for development of f-IDH, with a p value of 0.018. After controlling for sex and age, the use of CCB and ACE-inhibitor appears to be protective against f-IDH, though the P values at 0.465 and 0.273 respectively, were insignificant. The small number of patients after matching for age and sex may be the reason for not noting a significant difference. Tisler et al⁵⁰ found that the use of CCB and ACE-I as anti-hypertensive drugs was associated with reduced risk of frequent IDH events, with a significant P value of <0.05 for either drug. The difference may also arise depending on whether one is using higher doses of ACE-I for purposes of blood pressure control with consequent vasodilatation or low doses that protect against myocardial remodeling.

The mean haemoglobin of 8.55g/dL (± 1.29) for the study subjects was low. The acceptable level of haemoglobin is >12g/dL. The difference in haemoglobin level between patients with f-IDH and those with occasional or no IDH was statistically insignificant ($P=0.726$). The fact that most patients in the study had anaemia may be responsible for the lack of difference between the two groups. While all patients with ESRD require regular injections of recombinant erythropoetin, only a few get it because of costs.

There was no significant difference between the serum calcium level between patients with f-IDH (1.96 ± 0.26 mmol/L) and those with occasional or no IDH (2.04 ± 0.27 mmol/L). This result differs from those reported in

other studies where it was found that low serum calcium is a risk factor for IDH^{29,30}. The mean serum calcium was generally lower in the whole study population and this may be the reason why no significant difference was noted between the two groups. Vitamin D3 is not regularly used in ESRD patients with hypocalcaemia at the KNH renal Unit because of costs.

Our study found an insignificant difference in serum level of phosphorous between patients with f-IDH and those with occasional or no IDH events. This finding is unlike those of Tisler et al⁵⁰, who in a study of 956 patients, found higher phosphorous level to be a significant risk factor for frequent IDH ($p < 0.005$). The mean phosphorous level for all patients was higher in this study.

This study found lower mean serum albumin in patients with f-IDH ($36.80 \pm 4.82 \text{g/L}$) as compared to that in patients with occasional or no IDH ($38.98 \pm 4.1 \text{g/L}$) though with an insignificant P value of 0.098. The difference was statistically significant ($P = 0.016$), after matching the patients for sex and age to the nearest five years. Degoulet et al⁴, in a study of 1110 patients, found low predialysis plasma protein to be a risk factor for symptomatic hypotension. Ultrafiltration during haemodialysis draws volume from the haemodynamically active central circulation, whereas most of the volume overload resides in the intercellular compartment. Oncotic pressure gradient between capillaries and interstitial space affects refill. Low albumin leads to low oncotic pressure, increasing the risk for IDH.

On echocardiographic evaluation of the heart, mean LV ejection fraction (E/F) for study subjects was found to be $62.57\% (\text{SD} \pm 16.80)$, with a range of 22% to 87.57%. After matching for age and sex the difference in LV ejection fraction between patients with frequent IDH and those with

occasional or no IDH was statistically insignificant with a P value of 0.721. Previous studies by Wizemann et al ¹¹, and Punzengruber et al ¹², have shown no relationship between LV systolic function and intradialysis hypotension events. Generally patients with concentric LV hypertrophy, a common feature of ESRD, have normal ejection fraction.

LV diastolic dysfunction was present in 73.7% of the patients with frequent IDH and 61.3% of those with occasional or no IDH, with a statistically significant difference at a P value of 0.024. After matching for age and sex, the difference was statistically insignificant (P= 0.079). A previous study by Ruffinmann et al ¹⁵, found that LV diastolic dysfunction is a risk factor for intradialysis hypotension. Cardiac output in a patient with reduced compliance is dependent on diastolic filling volume and pressure. During dialysis intravascular volume is reduced because of extra corporeal circulation and ultrafiltration predisposing the patients to hypotension.

CONCLUSION

1. There is a high period prevalence of frequent intradialysis hypotension in patients on chronic haemodialysis at KNH renal unit.
2. Diabetes mellitus as the underlying cause of ESRD is associated with f-IDH in patients on chronic haemodialysis as a form of renal replacement therapy.
3. Elderly patients are the most at risk for frequent intradialysis hypotension events.
4. Sixty-six percent of the patients on chronic haemodialysis have left ventricular diastolic dysfunction and are at more risk of intradialysis hypotension.
5. Low serum albumin is a risk factor for development of f-IDH.

Study limitation

The study relied on retrospective information from dialysis records for identifying IDH events. Though the records are well kept and all events and procedures recorded, the information cannot be as reliable as that obtained prospectively.

From the study, it is only possible to associate various variables with IDH but not establish cause-effect.

RECOMMENDATIONS

1. All patients with end-stage renal disease should have echocardiographic evaluation of cardiac function with emphasis on LV diastolic function before initiation of haemodialysis.
2. Elderly patients require more careful monitoring and management, as they are at more risk of developing intradialysis hypotension.
3. Management of anaemia in patients with ESRD on chronic haemodialysis at KNH renal unit needs re-evaluation.
4. A prospective study to look at risk factors for morbidity and mortality in patients with ESRD at KNH renal unit is required.

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Appendix I

Consent form

INTRADIALYSIS HYPOTENSION IN PATIENTS WITH ESRD ON CHRONIC HAEMODIALYSIS.

Dear sir/madam

I, Dr. Awiki Chalopa, kindly request you to participate in a study that aims at determining the prevalence and risk factors for intradialysis hypotension at KNH renal unit. IDH causes a lot of discomfort to a patient because of associated symptoms such as nausea, vomiting, cramps, headaches and dizziness. Its management is expensive to the renal unit as it consumes a lot of staff time and financial resources. It is hoped that results of this study will help in reducing the incidence of IDH.

Participation is on voluntary basis and you can withdraw from the study at any stage. Withdrawal will not interfere with your treatment in anyway. 5mls of blood will be taken from you for determination of haemoglobin level, serum calcium, Potassium, sodium, phosphate and albumin. Your cardiac functions will be assessed using an echocardiogram machine.

Blood samples will be used only for the intended purposes.

Expected risk

Mild, bearable pain during blood sampling.

Confidentiality

Any information volunteered to the researcher will be treated in confidence.

Appendix II

INTRADIALYSIS HYPOTENSION IN PATIENTS WITH ESRD ON CHRONIC HAEMODIALYSIS.

Dear sir/madam

Thank you for accepting to participate in this very important study. By so doing you have agreed to be a key partner in a scientific process which is hoped to positively impact in the management of dialysis patients. Please kindly give answers to a series of questions that I will read to you. Hopefully you will do this to the best of your ability.

Thank you for accepting to spare your valuable time.

Dr. Awiki Chalopa (principal Investigator)

Appendix III

Declaration form

I _____
Do hereby agree voluntarily to participate in this research on intradialysis
hypotension in patients with renal failure details of which have been
explained to me by Dr. Awiki Chalopa.

Signed _____
(Participant)

Witness/researcher _____

Dated _____

Appendix V

Name	IP no.	Group	Study no.
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	Serum				
	Ca	K	Na	Albumin	Phosphate

Haemoglobin level

Dry weight	Weight before Echo
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Echocardiography findings

LV Dd	LV Sd	EF
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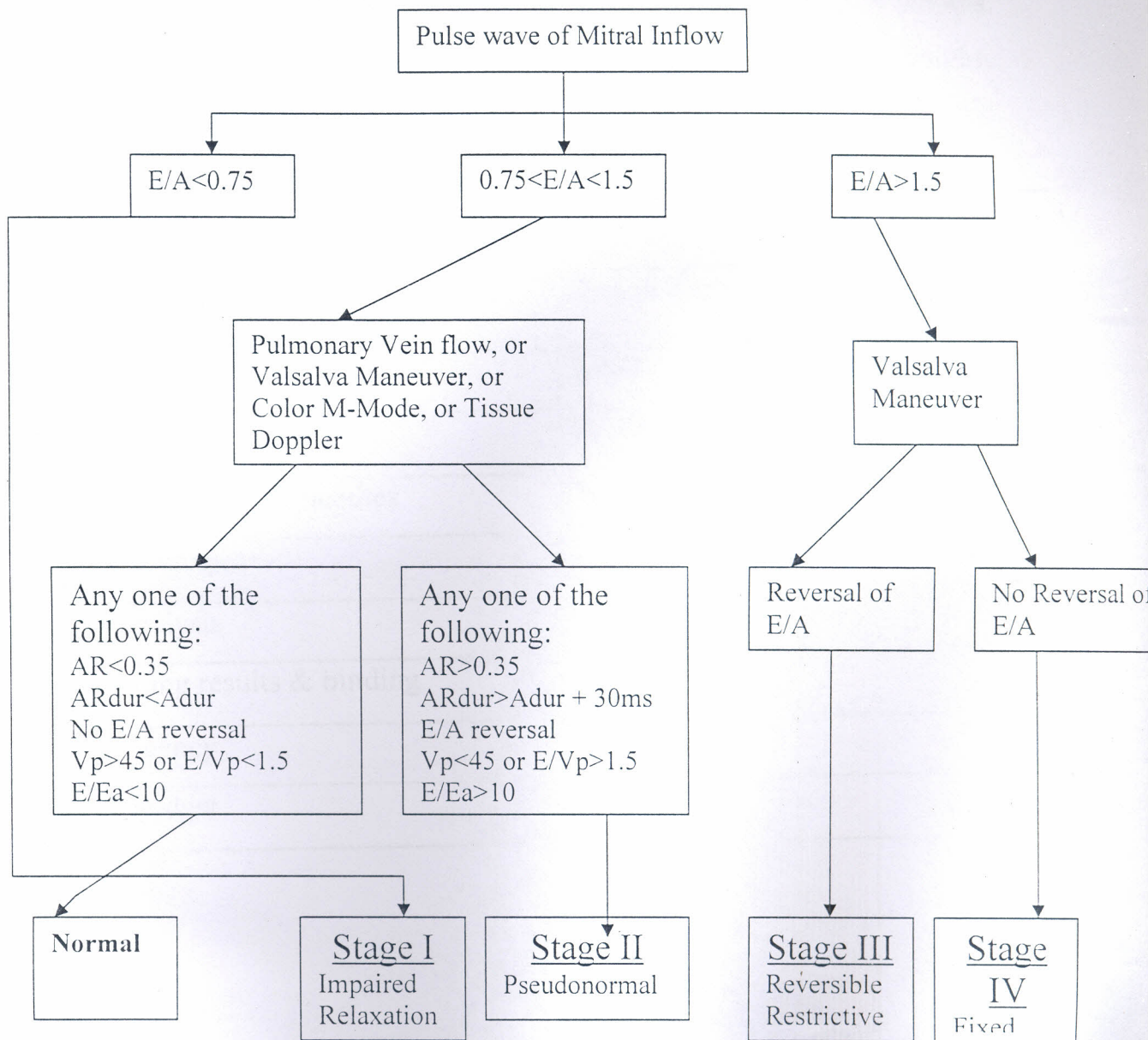
Mitral E -----m/sec. A-----m/sec. E/A ratio-----	E deceleration time
Valsalva E----m/sec. A-----m/sec. E/A ratio-----	

Diastolic function

Echo conclusion

Appendix VI

Diastolic Function Evaluation



The above Diagram illustrates practical echocardiographic approach to evaluation of diastolic function. A, Peak late diastolic transmitral flow velocity; Adur, duration of A wave; AR, peak pulmonary venous atrial reversal flow velocity; ARdur, AR duration; E, peak early diastolic transmitral flow velocity; Ea, peak early diastolic myocardial velocity; VP, flow propagation velocity.

Budget & duration of study

Protocol preparation-----	6 months.
Study approval-----	2 months.
Data collection-----	2 months.
Data analysis & presentation-----	2 months.

Item	Cost in Kenya shillings
Protocol preparation	5,000
Laboratory analysis	24,000
Bottles, syringes & needles	2,000
ECG & Echoes	120,000
Data analysis	5,000
Compiling results & binding	10,000
Contingency	24,900
Total budget	190,900

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