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Hon-Chun Hsu; Chanel Robinson; Gavin Norton; Angela Woodiwiss; Patrick Dessein

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ORIGINAL RESEARCH

The Optimal Haemoglobin Target in Dialysis Patients May Be Determined by Its Contrasting Effects on Arterial Stiffness and Pressure Pulsatility

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Hon-Chun Hsu[1,2]
Chanel Robinson[1]
Gavin R Norton[1]
Angela J Woodiwiss[1]
Patrick H Dessein[1,3,4]

[1]Cardiovascular Pathophysiology and Genomics Research Unit, School of Physiology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; [2]Nephrology Unit, Milpark Hospital, Johannesburg, South Africa; [3]Internal Medicine Department, University of the Witwatersrand, Johannesburg, South Africa; [4]Free University and University Hospital, Brussels, Belgium

Introduction: It remains unclear why the optimal haemoglobin target is lower in patients with chronic kidney disease (CKD) than in non-CKD persons. Arteriosclerosis and consequent impaired arterial function comprise a central cardiovascular risk mechanism in CKD. We hypothesized that the optimal haemoglobin target depends on its opposing effects on arterial stiffness and pressure pulsatility in CKD.

Methods: Arterial stiffness (aortic pulse wave velocity), wave reflection (augmentation index, reflected wave pressure and reflection magnitude), and pressure pulsatility (central systolic and pulse pressure, peripheral pulse pressure, pressure amplification and forward wave pressure) were assessed in 48 dialysis patients.

Results: In established confounder and diabetes adjusted linear regression models, haemoglobin levels were directly associated with arterial stiffness (partial R=0.366, p=0.03) and inversely with central systolic pressure (partial R=−0.344, p=0.04), central pulse pressure (partial R=−0.403, p=0.01), peripheral pulse pressure (partial R=−0.521, p=0.001) and forward wave pressure (partial R=−0.544, p=0.001). The presence of heart failure and use of angiotensin converting enzyme inhibitors or angiotensin receptor blockers and erythropoietin stimulating agents did not materially alter these relationships upon further adjustment for the respective characteristics in the models, and in sensitivity analyses. In receiver operator characteristic curve analysis, the optimal haemoglobin concentration cut-off values in predicting arterial stiffness and increased central pulse pressure were remarkably similar at 10.95 g/dl and 10.85 g/dl, respectively, and with clinically useful sensitivities, specificities and positive and negative predictive values. In logistic regression models, a haemoglobin value of >10.9 mg/dl was associated with both arterial stiffness (>10 m/sec; OR (95% CI) = 10.48 (1.57–70.08), p=0.02) and normal central pulse pressure (>50 mmHg; OR (95% CI) = 7.55 (1.58–36.03), p=0.01).

Conclusion: This study suggests that the optimal haemoglobin target in dialysis patients is ~11g/dl and determined by its differential and contrasting effects on arterial stiffness and pressure pulsatility.

Keywords: haemoglobin target, dialysis, arterial stiffness, pressure pulsatility

Introduction

Arteriosclerosis encompasses hypertrophy and fibrosis of the medial layer in large arteries.[1] Chronic kidney disease (CKD) is characterized by marked premature arteriosclerosis that causes impaired arterial function.[2–4] Arterial stiffness results in an accelerated forward wave, which increases central systolic blood pressure and

Correspondence: Patrick H Dessein
80 Scholtz Road, Norwood, Johannesburg 2117, South Africa
Email patrick.dessein22@gmail.com

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enhances wave reflection that occurs at bifurcations and due to changes in composition and progressive narrowing of the vessels along the arterial tree. The increased reflected wave arrives earlier at the heart, ie in systole rather than diastole, and thereby reduces diastolic blood pressure and coronary perfusion. The increased forward and reflected waves enhance pressure pulsatility and decrease pulse pressure amplification, which increases transmission of pulsatile pressure into the microcirculation leading to CKD progression. Increased arterial stiffness, wave reflection and pressure pulsatility thereby each contribute to cardiovascular event rates including heart failure, arrhythmias, stroke and myocardial infarction in CKD.[3,5,6]

Accelerated arteriosclerosis in CKD is mediated by adverse traditional as well as non-traditional or renal impairment specific cardiovascular risk factors.[2–7]

In observational studies, anaemia is associated with CVD in CKD.[8] However, the optimal haemoglobin target in CKD patients is reportedly substantially lower in CKD compared to non-CKD individuals.[9,10] Indeed, treatment with erythropoietin stimulating agents in CKD patients is associated increased CVD events when a haemoglobin level of ~13 g/dl is targeted.[11,12] In this regard, nitric oxide reduces arterial stiffness and peripheral vascular resistance[13] whereas haemoglobin is a potent nitric oxide scavenger.[14] High haemoglobin levels are associated with arterial stiffness in non-CKD persons.[15–17] Other investigations in persons with and without CKD indicate that anaemia increases pressure pulsatility.[18,19] In the present study, we therefore hypothesized that the optimal haemoglobin target in CKD may depend on its contrasting effects on arterial stiffness and pressure pulsatility in CKD. We assessed the independent relationships of haemoglobin levels with arterial function measures including pulse wave velocity, wave reflection and pressure pulsatility in a cohort of dialysis patients.

Patients and Methods

Patients

Forty-eight dialysis patients were enrolled at the Milpark Hospital in Johannesburg, South Africa. Patients with infection or/and active cancer were excluded. This study was performed according to the Helsinki Declaration of 1975 as revised in 2013 and was approved by the University of the Witwatersrand Human (Medical) research Ethics Committee (protocol number: M15-08-43) in Johannesburg, South Africa. Written informed consent was obtained in each patient prior to participation.

Methods

The recorded characteristics included demographic features, lifestyle factors, anthropometric measures, traditional and non-traditional cardiovascular risk factors, the presence of established cardiovascular disease including heart failure, arterial function and other hemodynamic characteristics that included systemic vascular resistance, stroke volume and work, cardiac output and left ventricular mass index. Data recording was performed on the day prior to undergoing dialysis, which was applied thrice weekly in each of these patients.

Cardiovascular Risk Factors

We recorded traditional and non-traditional or renal cardiovascular risk factors as previously reported[20] and given in the online Supplementary Material. For the present study, high phosphate was considered present when the phosphate concentration was >1.42 mmol/l or/and phosphate lowering drugs including calcium carbonate or sevelamer therapy in 44 and 1 patients, respectively, was employed. Mean arterial blood pressure for the peripheral waveform was determined electronically by the SphygmoCor device (see below) and using the formula

$$MP = \frac{\sum_{i=T_0}^{T_F} P_i}{n}$$

where T_0=start of the waveform; T_F=end of waveform; P_i=pressure points and n=number of pressure points.

Established Cardiovascular Disease

Ischemic heart disease, heart failure and cerebrovascular and peripheral arterial disease that was confirmed by a cardiologist, neurologist and vascular surgeon, respectively, comprised recorded established cardiovascular disease.

Arterial Function

Applanation tonometry and SphygmoCor software were used to determine central hemodynamic features as previously reported[20] and given in the online Supplementary Material. We assessed aortic pulse wave velocity, augmentation index, reflected wave pressure and reflection magnitude, central systolic and pulse pressure, peripheral pulse pressure, pressure amplification and forward wave pressure.

Other Hemodynamic Parameters

Echocardiography was performed as recommended by the American Society of Echocardiography convention and

using a Sonosite M-Turbo ultrasound (SonoSite® Inc., Bothell, WA, USA).[21] We assessed stroke volume, cardiac output and left ventricular mass index. Further details are given in the online Supplementary Material. Systemic vascular resistance was calculated from mean arterial pressure and cardiac output according to the equation mean arterial pressure=systemic vascular resistance x cardiac output assuming that right atrial pressure=0 mmHg. Stroke work was calculated as stroke volume x systolic blood pressure x 0.0144, and expressed in gram-meters/beat.

Data Analysis

Statistical analysis was performed on IBM SPSS statistics program (version 23.0 IBM, USA) and significance was set at $p \leq 0.05$. Results are expressed as mean (SD) or median (interquartile range, IQR) for continuous variables and percentages for categorical variables. Logarithmic transformation was applied when non-normally distributed data were analysed in multivariable regression models.

The associations of lifestyle factors, anthropometric measures and major traditional and non-traditional/renal cardiovascular risk factors with arterial function parameters were first assessed in established confounder[20,22] including age, sex, race, weight, height, heart rate and mean arterial blood pressure adjusted linear regression models.

Subsequently, the independent associations of recorded cardiovascular risk factors with arterial function parameters were assessed by entering established confounders together with those that were related to arterial function in the previous analysis into single models.

As heart failure[23] and treatment with angiotensin converting enzyme inhibitors or angiotensin blockers[24] as well erythropoietin stimulating agents[25] can also impact arterial function, the potential influence of the respective factors was assessed in separate models and sensitivity analyses.

The above mentioned analyses revealed that haemoglobin concentrations were directly associated with arterial stiffness and inversely related to pressure pulsatility. We therefore investigated the respective relationships further by performing receiver operator characteristic (ROC) curve analysis.

Finally, we assessed bivariate associations among haemoglobin concentrations and other hemodynamic characteristics by determining Pearson correlation coefficients.

Results

Patient Characteristics

The recorded characteristics are given in Table 1. The mean (SD) age was 55.8 (14.3) years and 22 (45.8%) were women. More than half of the study participants (56.3%) were of black population origin. Hypertension, dyslipidemia and diabetes were present in 44 (91.7%), 30 (71.4%) and 19 (39.6%), respectively. Angiotensin converting enzyme inhibitors or angiotensin receptor blockers and erythropoietin stimulating agents were used in 37 (77.1%) and 43 (89.6%) of the patients, respectively. Among those with cardiovascular disease (n=14 (29.6%)), 7 (14.6%) had heart failure. The pulse wave velocity and left ventricular mass index were both large with a median (interquartile range) and mean (SD) value of 11.2 (7.8–14.9) and 103.4 (51.0), respectively.

Associations of Haemoglobin Concentrations with Arterial Function

As given in Table 2, in age, sex, race, weight, height, mean blood pressure and heart rate adjusted linear regression models, haemoglobin levels were directly associated with pulse wave velocity (p=0.05) and inversely with central systolic blood pressure (p=0.03), central pulse pressure (p=0.01), peripheral pulse pressure (p=0.001) and forward wave pressure (p=0.001) (model 1 in Table 2).

Apart from diabetes that was associated with pulse wave velocity (p=0.01), augmentation index (p=0.01), reflected wave pressure (p=0.02), reflection magnitude (p=0.02) and central pulse pressure (p=0.02), and heart rate and mean blood pressure for which data are not shown as these characteristics were included as established confounders in the models, none of the other traditional and non-traditional /renal risk factors as given in Table 1 were associated with arterial function parameters. Model 2 in Table 2 shows that upon additional adjustment for diabetes, haemoglobin concentrations remained associated with pulse wave velocity (p=0.03), central systolic blood pressure (p=0.04), central pulse pressure (p=0.01), peripheral pulse pressure (p=0.001) and forward wave pressure (p=0.001).

When we additionally adjusted for the presence of heart failure (model 3 in Table 2), the associations of haemoglobin concentrations with arterial function remained consistent (p=0.03, p=0.04, p=0.01, p=0.001 and p=0.002 for pulse wave velocity, central systolic blood pressure, central pulse pressure, peripheral pulse pressure and forward wave pressure, respectively.

Table 1 Recorded Patient Characteristics in 48 Dialysis Patients

Demographics			
Age (years)	55.8 (14.3)	Dialysis duration (months)	24 (12–36)
Female sex	22 (45.8)	Phosphate (mmol/l)	1.4 (0.9–1.8)
Black	27 (56.25)	Calcium (mmol/l)	2.3 (2.1–2.4)
Asian	11 (22.92)	Calcium x phosphate	3.0 (2.2–4.0)
Mixed	6 (12.5)	Phosphate binder use	35 (79.5)
White	4 (8.33)	High phosphate	44 (83.3)
Lifestyle		IPTH	470.3 (182.0–785.8)
Alcohol use (units per week)	1 (2.1)	High sensitivity CRP (mg/l)	8.9 (2.5–29.9)
Current smoker	0 (0)	Haemoglobin (g/dl)	10.8 (1.7)
Ex-smoker	4 (8.3)	Transferrin saturation (%)	22.9 (19.1–28.9)
Anthropometry		Ferritin (ng/mL)	361 (128–654)
Body mass index (kg/m^2)	26.8 (5.6)	Albumin (g/l)	37.9 (6.5)
Waist (cm)	99 (16)	Vitamin D (nmol/l)	19.7 (9.0)
Waist-hip ratio	0.98 (0.09)	Uric acid (mmol/l)	0.28 (0.12)
Weight (kg)	74.7 (14.7)	ESA use	43 (89.6)
Height (m)	1.67 (0.11)	**Cardiovascular disease**	14 (29.2)
Waist-height ratio	0.60 (0.11)	Heart Failure	7 (14.6)
Major traditional risk factors		**Arterial function**	
Hypertension	44 (91.7)	Pulse wave velocity (m/sec)	11.2 (7.8–14.9)
Systolic BP (mmHg)	146 (22)	Augmentation index (%)	27.1 (16.2)
Diastolic BP (mmHg)	85 (14)	Reflected wave pressure (mmHg)	25.0 (15.0–29.5)
Mean BP	105 (14)	Reflection magnitude (%)	67.0 (16.6)
Heart rate (beats/min)	75 (17)	Central systolic BP (mmHg)	136 (22)
Dyslipidemia	30 (71.4)	Central pulse pressure (mmHg)	49 (17)
Total cholesterol (mmol/l)	4.3 (1.1)	Pulse pressure amplification	132 (29)
LDL cholesterol (mmol/l)	2.4 (1.0)	Forward wave pressure (mmHg)	35 (11)
HDL cholesterol (mmol/l)	1.13 (0.90–1.55)	**Other hemodynamics**	
Non-HDL cholesterol (mmol/l)	3.1 (1.0)	Stroke volume (mL/beat)	71.4 (26.0)
Triglycerides (mmol/l)	1.33 (0.88–1.80)	Cardiac output (l/min)	5.5 (2.2)
Diabetes	19 (39.6)	Stroke work (gram-meters/beat)	153.2 (66.8)
ACEI/ARB therapy	37 (77.1)	Left ventricular mass index (g/m2)	103.4 (51.0)
Non-traditional/renal risk factors		SVR (mmHg/l/min)	20.4 (15.2–24.3)

Notes: Data are expressed as mean (SD), median (interquartile range) or number (%).
Abbreviations: BP, blood pressure; LDL, low density lipoprotein; HDL, high density lipoprotein; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; iPTH, intact parathyroid hormone; CRP, C-reactive protein; ESA, erythropoietin stimulating agent; SVR, systemic vascular resistance.

As shown in model 4 in Table 2, upon additional adjustment for the use of angiotensin converting enzyme inhibitors or angiotensin receptor blockers, haemoglobin concentrations remained associated with pulse wave velocity (p=0.03), peripheral pulse pressure (p=0.002) and forward wave pressure (p=0.005) but their relationships with central systolic blood pressure and central pulse pressure no longer reached significance (p=0.1 and p=0.06, respectively.

As given in model 5 in Table 2, when we additionally adjusted for treatment with erythropoietin stimulating agents, haemoglobin levels remained associated with pulse wave velocity (p=0.03), central systolic blood pressure (p=0.04), central pulse pressure (p=0.01), peripheral pulse pressure (p=0.001) and forward wave pressure (p=0.001).

Associations of Haemoglobin Concentrations with Arterial Function in Sensitivity Analyses

To further assess whether the presence of heart failure and angiotensin converting enzyme inhibitor or angiotensin receptor blocker and erythropoietin stimulating agent therapy could influence the impact of haemoglobin concentrations on arterial function, we performed sensitivity analyses. These results are shown in Table 3.

In patients without heart failure (n=41), haemoglobin levels were associated with pulse wave velocity (p=0.01), central pulse pressure (p=0.02), peripheral pulse pressure (p=0.004) and forward wave pressure

Table 2 Associations of Haemoglobin Concentrations with Arterial Function in 48 Dialysis Patients

	Model 1[a]				Model 2[b]				Model 3[c]				Model 4[d]				Model 5[e]			
Arterial Function Parameter	**β (SD)**	**Partial R**	***P***	**Model R^2**	**β (SD)**	**Partial R**	***P***	**Model R^2**	**β (SD)**	**Partial R**	***P***	**Model R^2**	**β (SD)**	**Partial R**	***P***	**Model R^2**	**β (SD)**	**Partial R**	***P***	**Model R^2**
Log PWV	**0.030 (0.015)**	**0.329**	**0.05**	**0.314**	**0.031 (0.014)**	**0.366**	**0.03**	**0.450**	**0.031 (0.014)**	**0.378**	**0.03**	**0.476**	**0.031 (0.014)**	**0.375**	**0.03**	**0.468**	**0.031 (0.014)**	**0.374**	**0.03**	**0.461**
Aix	1.835 (1.215)	0.232	0.1	0.552	1.920 (1.183)	0.284	0.1	0.589	1.954 (1.192)	0.291	0.1	0.589	1.946 (1.220)	0.293	0.1	0.588	1.920 (1.192)	0.238	0.1	0.597
Log RWP	−0.027 (0.014)	−0.322	0.07	0.552	−0.026 (0.014)	−0.323	0.07	0.586	−0.026 (0.014)	−0.321	0.08	0.587	−0.020 (0.014)	−0.262	0.2	0.613	−0.026 (0.014)	−0.324	0.08	0.588
Rm	1.951 (1.226)	0.275	0.1	0.430	2.044 (1.184)	0.301	0.1	0.592	2.076 (1.194)	0.307	0.09	0.599	1.995 (1.224)	0.299	0.1	0.582	2.052 (1.190)	0.305	0.1	0.601
CSBP	**−2.231 (1.035)**	**−0.347**	**0.03**	**0.798**	**−2.150 (1.022**	**−0.344**	**0.04**	**0.809**	**−2.151 (1.038)**	**−0.344**	**0.04**	**0.809**	−1.514 (1.091)	−0.246	0.1	0.816	**−2.153 (1.039)**	**−0.344**	**0.04**	**0.810**
CPP	**−3.126 (1.227)**	**−0.400**	**0.01**	**0.541**	**−3.005 (1.189)**	**−0.403**	**0.01**	**0.583**	**−3.004 (1.208)**	**−0.402**	**0.01**	**0.583**	−2.357 (1.208)	−0.336	0.06	0.480	**−3.003 (1.208)**	**−0.402**	**0.01**	**0583**
PPP	**−5.828 (1.616)**	**−0.510**	**0.001**	**0.390**	**−5.831 (1.589)**	**−0.521**	**0.001**	**0.426**	**−5.807 (1.612)**	**−0.520**	**0.001**	**0.426**	**−5.570 (1.670)**	**−0.502**	**0.002**	**0.424**	**−5.599 (1.611)**	**−0.506**	**0.001**	**0.43**
PPamp	−2.838 (2.138)	−0.222	0.2	0.502	−2.856 (2.173)	−0.223	0.2	0.502	−2.851 (2.206)	−0.223	0.2	0.503	−3.531 (2.280)	−0.272	0.1	−0.530	−2.939 (2.160)	−0.234	0.1	0.524
FWP	**−3.111 (0.862)**	**−0.544**	**0.001**	**0.480**	**−3.087 (0.870)**	**−0.544**	**0.001**	**0.489**	**−3.080 (0.884)**	**−0.543**	**0.002**	**0.490**	**−2.658 (0.858)**	**−0.512**	**0.005**	**0.546**	**−3.091 (0.880)**	**−0.546**	**0.001**	**0.49**

Notes: Significant associations are shown in bold. [a]Adjusted for age, sex, race, height, weight, mean arterial pressure and heart rate. [b]Adjusted for age, sex, race, height, weight, mean arterial pressure, heart rate and diabetes. [c]Adjusted for age, sex, race, height, weight, mean arterial pressure, heart rate, diabetes and heart failure. [d]Adjusted for age, sex, race, height, weight, mean arterial pressure, heart rate, diabetes and angiotensin converting enzyme inhibitor or angiotensin receptor blocker therapy. [e]Adjusted for age, sex, race, height, weight, mean arterial pressure, heart rate, diabetes and erythropoietin stimulating agent therapy.

Abbreviations: β, regression coefficient; Log, logarithmically transformed; PWV, pulse wave velocity; Aix, augmentation index; RWP, reflected wave pressure; Rm, reflection; magnitude; CSBP, central systolic blood pressure; CPP, central pulse pressure; PPP, peripheral pulse pressure; PPamp, pulse pressure amplification; FWP, forward wave pressure.

Table 3 Associations of Haemoglobin Concentrations with Arterial Function in Sensitivity Analyses Among Patients Without Heart Failure and on ACEI or ARB and ESA Agent Therapy

	Patients without Heart Failure (n=41)				**Patients on ACEI or ARB Therapy (n=37)**				**Patients on ESA Therapy (n=43)**			
Arterial Function Parameter	**β (SD)**	**Partial R**	***P***	**Model R^2**	**β (SD)**	**Partial R**	***P***	**Model R^2**	**β (SD)**	**Partial R**	***P***	**Model R^2**
Log PWV	**0.037 (0.015)**	**0.435**	**0.01**	**0.390**	0.031 (0.017)	0.357	0.07	0.440	**0.031 (0.014)**	**0.376**	**0.03**	**0.409**
Aix	2.347 (1.212)	0.355	0.06	0.621	1.792 (1.399)	0.269	0.2	0.519	**2.097 (1.030)**	**0.365**	**0.05**	**0.677**
Log RWP	−0.020 (0.014)	−0.264	0.2	0.550	−0.027 (0.016)	−0.350	0.1	0.643	−0.026 (0.014)	−0.327	0.08	0.537
Rm	**2.509 (1.203)**	**0.378**	**0.04**	**0.626**	1.861 (1.405)	0.278	0.2	0.512	**2.225 (1.015)**	**0.389**	**0.03**	**0.687**
CSBP	1.971 (1.017)	−0.334	0.07	0.796	−1.994 (1.159)	−0.338	0.09	0.824	−2.149 (1.051)	0.239	0.1	0.773
CPP	**−2.809 (1.212)**	**−0.407**	**0.02**	**0.555**	**−2.697 (1.230)**	**−0.416**	**0.03**	**0.644**	**−3.011 (1.244**	**0.404**	**0.02**	**0.535**
PPP	**−5.476 (1.723)**	**−0.508**	**0.004**	**0.382**	**−6.344 (1.807)**	**−0.567**	**0.002**	**0.447**	**−5.406 (1.763)**	**−0.482**	**0.004**	**0.336**
PPamp	−2.862 (2.484)	−0.216	0.3	0.496	−4.199 (2.764)	−0.302	0.1	0.525	−3.149 (2.091)	−0.265	0.1	0.557
FWP	**−2.888 (0.922)**	**−0.524**	**0.004**	**0.437**	**−2.190 (2.008)**	**−0.588**	**0.003**	**0.587**	**−3.125 (0.903)**	**−0.554**	**0.002**	**0.445**

Notes: Associations were assessed in age, sex, race, weight, height, heart rate, mean arterial pressure and diabetes adjusted linear regression models. Significant associations are shown in bold.

Abbreviations: β, regression coefficient; Log, logarithmically transformed; PWV, pulse wave velocity; Aix, augmentation index; RWP, reflected wave pressure; Rm, reflection magnitude; CSBP, central systolic blood pressure; CPP, central pulse pressure; PPP, peripheral pulse pressure; PPamp, pulse pressure amplification; FWP, forward wave pressure.

(p=0.004) whereas their relationship with central systolic blood pressure did not reach significance (p=0.07). Haemoglobin concentrations were further directly associated with reflection magnitude (p=0.04). When the mean arterial pressure was replaced by systemic vascular resistance in the respective model, the association of haemoglobin levels with reflection magnitude was not materially altered (partial R=0.334, p=0.08).

Among patients on angiotensin converting enzyme inhibitor or angiotensin receptor blocker therapy, haemoglobin levels were associated with central pulse pressure (p=0.03), peripheral pulse pressure (0.002) and forward wave pressure (p=0.003) but their relationship with pulse wave velocity and central systolic blood pressure did not reach significance (p=0.07 and p=0.09, respectively).

In patients treated with erythropoietin stimulating agents, haemoglobin concentrations were associated with pulse wave velocity (p=0.03), central pulse pressure (p=0.02), peripheral pulse pressure (p=0.004) and forward wave pressure (p=0.002) whereas their relationship with central systolic blood pressure did not reach significance (p=0.1). Haemoglobin levels were further associated with augmentation index (p=0.05) and reflection magnitude (p=0.03). When the mean arterial pressure was replaced by systemic vascular resistance in the respective model, the association of haemoglobin levels with reflection magnitude was not materially altered (partial R=0.317, p=0.1).

Haemoglobin Concentrations, Arterial Stiffness and Increased Central Pulse Pressure

Arterial stiffness (pulse wave velocity >10 m/sec)[26,27] and increased pulse pressure (>50 mmHg)[28] were recorded in 46.3% and 28.7% of the patients, respectively. Given the independent associations of haemoglobin concentrations with arterial stiffening and low pressure pulsatility among these patients (Table 2), we determined the accuracy of haemoglobin concentrations in predicting arterial stiffness and a normal central pulse pressure in ROC curve analysis. This is shown in Figure 1. The area under the curve (AUC) of the ROC curve was associated with arterial stiffness (Figure 1A; AUC=0.670) and normal pulse pressure (Figure 1B; AUC=0.717). To estimate the optimal cut-off values for haemoglobin concentrations in determining arterial function, we calculated the Youden index. The optimal haemoglobin concentration cut-off value in predicting the presence of arterial stiffness was 10.95 g/dl with a corresponding sensitivity, specificity, and positive and negative predictive value as determined by applying Bayes' theorem of 45.7%, 77.8%, 84.8% and 60.9%, respectively; the optimal haemoglobin concentration cut-off value in predicting the presence of a normal pulse pressure was 10.85 g/dl with a corresponding sensitivity, specificity, and positive and negative predictive value of 72.7%, 81.8%, 77.1% and 78.0%, respectively.

A haemoglobin value of >10.9 mg/dl was associated with arterial stiffness (OR (95% CI) = 4.77 (1.23–18.53), p=0.02) and normal central pulse pressure (OR (95% CI) = 7.88 (1.96–31.57), p=0.004). In established confounder adjusted logistic regression models, a haemoglobin value of >10.9 mg/dl remained associated with arterial stiffness (OR (95% CI) = 10.48 (1.57–70.08), p=0.02) and normal central pulse pressure (OR (95% CI) = 7.55 (1.58–36.03), p=0.01).

Associations Among Haemoglobin Levels and Other Haemodynamic Characteristics

Associations among haemoglobin concentrations and other hemodynamic characteristics are given in Table 4. Haemoglobin levels were directly associated with systemic vascular resistance (p=0.05) and inversely related to stroke volume (p=0.05), cardiac output (p=0.03) and stroke work (p=0.01). Systemic vascular resistance was inversely associated with stroke volume (p<0.0001), cardiac output (p<0.0001), stroke work and left ventricular mass index (p=0.01). Stroke volume was directly associated with cardiac output (p<0.0001), stroke work (p=0.01) and left ventricular mass index. Cardiac output was directly associated with stroke work (p<0.0001) and left ventricular mass index (p=0.005). Stroke work was directly associated with left ventricular mass index (p=0.02). Additionally, cardiac output was directly associated with pressure pulsatility measures including peripheral pulse pressure (R=0.340, p=0.02), central pulse pressure (R=0.299,

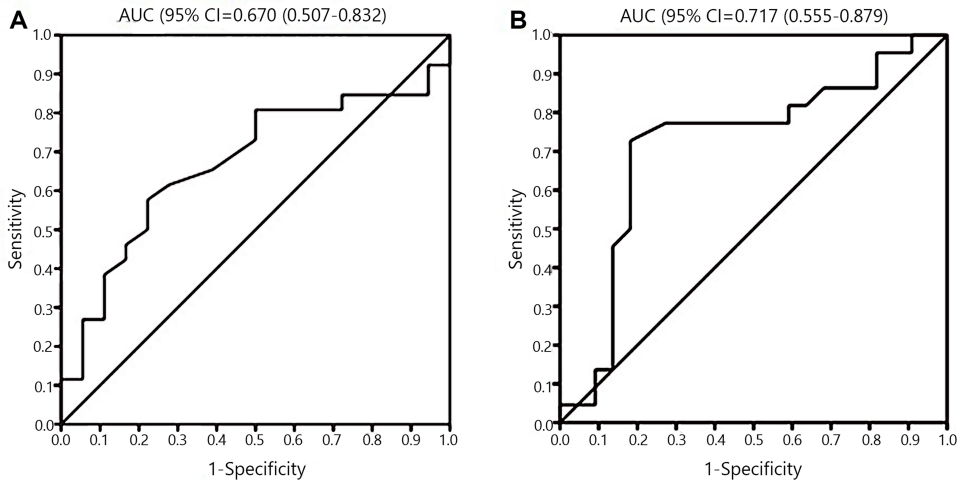

Figure 1 Receiver operator characteristic curves showing the accuracy of haemoglobin concentrations in predicting the presence of arterial stiffness (pulse wave velocity >10 m/sec) (**A**) and a normal central pulse pressure (<50 mmHg) (**B**).
Abbreviation: AUC, area under the curve.

Table 4 Bivariate Associations Among Haemoglobin Concentrations and Hemodynamic Variables

	Haemoglobin	Log SVR	Stroke Volume	Cardiac Output	Stroke Work	LVMI
Haemoglobin	–					
Log SVR	**0.285 (0.05)**	–				
Stroke volume	**−0.290 (0.05)**	**−0.869 (<0.0001)**	–			
Cardiac output	**−0.319 (0.03)**	**−0.926 (<0.0001)**	**0.910 (<0.0001)**	–		
Stroke work	**−0.367 (0.01)**	**−0.732 (<0.0001)**	**0.925 (<0.0001)**	**0.867 (<0.0001)**		
LVMI	−0.154 (0.3)	**−0.359 (0.01)**	**0.346 (0.01)**	**0.409 (0.005)**	**0.337 (0.02)**	–

Notes: Results are expressed as Pearson correlation (p). Significant associations are shown in bold.
Abbreviations: Log, logarithmically transformed; SVR, systemic vascular resistance; LVMI, left ventricular mass index.

p=0.05) and forward wave pressure (R=0.377, p=0.01), and tended to be directly associated with central systolic pressure (R=0.292, p=0.06).

Discussion

To our knowledge, this is the first study that simultaneously assessed the potential impact of haemoglobin concentrations on pulse wave velocity, wave reflection and pressure pulsatility as arterial function markers, as well as other hemodynamic characteristics in dialysis patients. The most striking and novel finding in this study was that haemoglobin concentrations were associated not only with arterial stiffness but also simultaneously with low pressure pulsatility measures including central systolic blood pressure, central and peripheral pulse pressure as well as forward wave pressure. In ROC curve analysis, the optimal haemoglobin concentration cut-off values in predicting arterial stiffness and increased central pulse pressure were remarkably similar at 10.95 g/dl and 10.85 g/dl respectively, and with clinically useful sensitivities, specificities and positive and negative predictive values. A haemoglobin value of >10.9 mg/dl was independently and strongly associated with both arterial stiffness (OR (95% CI) = 10.48 (1.57–70.08), p=0.02) and normal central pulse pressure (OR (95% CI) = 7.55 (1.58–36.03), p=0.01).

Anaemia is a highly prevalent comorbidity in dialysis patients.[29] Anaemia in CKD is mediated by multiple factors including reduced erythropoietin synthesis and release, iron deficiency and chronic inflammation.[30] Anaemia causes reduced viscosity and increased nitric oxide production and activation mediated vasodilatation and decreased peripheral vascular resistance.[18,31,32] Nitric oxide additionally reduces arterial stiffness, this to a larger extent than peripheral vascular resistance.[13] Haemoglobin is a potent nitric oxide scavenger.[14] The use of nitric oxide donors comprises a potential therapeutic intervention for arterial stiffness.[33] The vascular effects of anaemia or low haemoglobin result in reduced cardiac afterload, increased venous return, preload, left ventricular filling pressure and end-diastolic volume with consequent enhanced stroke volume and work. Increased stroke volume translates into enhanced cardiac output that is associated with enhanced pressure pulsatility.[34,35] Anaemia together with arterial stiffness thereby ultimately engender left ventricular hypertrophy and heart failure in CKD.[18,19] Our findings of a direct and concurrent inverse relationship of haemoglobin concentrations with arterial stiffness and pressure pulsatility measures, respectively, as well as the associations among haemoglobin levels and hemodynamic measures including systemic vascular resistance, stroke volume, stroke work, left ventricular mass index, cardiac output and pressure pulsatility parameters are each in keeping with these reported hemodynamic effects of anaemia in persons with and without CKD.

Our results are also in line with reported data in population and non-dialysis patient studies. The Korea National Health and Nutrition Examination Survey 2010–2012 revealed a relationship of anaemia with pulse pressure.[36] In the Chronic Renal Insufficiency Cohort Ancillary Study,[37] haemoglobin concentrations were inversely associated with peripheral pulse pressure. A direct association of haemoglobin concentrations with arterial stiffness has also been reported in two population studies[15,16] and patients with hypertension.[17]

In contrast to our findings, Schwartz and colleagues[38] previously reported in an inverse association between haemoglobin levels and aortic pulse wave velocity. The mean age (SD) age was 64.4 (15.8) years in the Schwarz study compared to 56.4 (13.3) years in ours. Notably, a high

aortic pulse wave velocity strongly predicts overall and cardiovascular mortality in end-stage renal disease among patients <60 years but loses its prognostic value in older patients.[39] The potential impact of age on haemoglobin-arterial function relationships in CKD merits further study. Wave reflection and pressure pulsatility were not explored in the Schwartz study.

Partial correction of severe anaemia targeting a haemoglobin level of 11.0 g/dl with erythropoietin stimulating agents in dialysis patients improves quality of life and reduces hospitalization and the need for transfusion.[40] However, recent meta-analyses have documented an increased risk of all-cause mortality, stroke, hypertension and vascular access thrombosis[11,12] when a normal haemoglobin level of ~13 g/dl is targeted with erythropoietin stimulating agents in CKD patients. The reason(s) why the optimal haemoglobin target as relates to CVD risk is lower in CKD compared to non-CKD individuals and the potential involved mechanisms remain largely unknown. Postulates include highly prevalent underlying atherosclerotic disease in CKD, increased viscosity and platelet aggregation, endothelial damage, vasoconstriction and increased peripheral vascular resistance.[30] Moreover, given the design of recent trials, the effect of a haemoglobin level of 11.5 to 13 g/dl on the vasculature in CKD patients is currently unknown.[9,10] Accordingly, the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guideline and a commentary on a recent meta-analysis state that targeting a haemoglobin level of 11.5 to 13 g/dl may still need to be considered in some CKD patients.[9,10] It is in this context that our findings in ROC curve analysis are particularly relevant as they indicate that a haemoglobin target of 10.9 g/dl in dialysis patients is associated with optimal arterial function comprising of a lower frequency of both arterial stiffness and increased pressure pulsatility. Taken together, the optimal haemoglobin target in CKD may be determined by its effects on arteriosclerosis, which is a key mechanism of increased CVD in CKD.[2,3] Notably, our results also suggest that the haemoglobin level reached is more important than the intervention used to reach the respective level.

Heart failure is associated with reduced pulse wave velocity and wave reflection.[23] Additionally, angiotensin converting enzyme inhibitors and angiotensin receptor blockers can improve arterial function,[24] and erythropoietin stimulating agents can impair nitric oxide production.[25] When we adjusted for these characteristics in separate models and performed sensitivity analyses, the partial R values for the haemoglobin-pulse wave velocity and haemoglobin-pressure pulsatility relations were materially unaltered. However, in sensitivity analyses, haemoglobin concentrations were additionally associated with reflection magnitude among patients without heart failure as well as in those using erythropoietin stimulating agents. Reduced nitric oxide activity is also implicated in increased wave reflection.[41] Interestingly, when we replaced mean arterial pressure by systemic vascular resistance in the respective models, the results were also materially unaltered. This suggests that potential effect of haemoglobin concentrations on reflection magnitude in dialysis patients is located centrally rather than at the peripheral or arteriolar level and is therefore unlikely to improve upon treatment with vasodilators.

Our study has limitations. Its design was cross-sectional, which precludes determining cause-effect relations. The numbers of patients, particularly in sensitivity analyses, were small. However, our main conclusions originated in comprehensively adjusted multivariable regression models. The strength of our study is that we performed a detailed evaluation of aortic function using SphygmoCor and other hemodynamic characteristics.

In conclusion, this study suggests that the optimal haemoglobin target in dialysis patients is ~11g/dl and determined by its differential and contrasting effects on arterial stiffness and pressure pulsatility.

Ethics Statement

This study was performed according to the Helsinki Declaration of 1975 as revised in 2013 and was approved by the University of the Witwatersrand Human (Medical) research Ethics Committee (protocol number: M15-08-43) in Johannesburg, South Africa. Written informed consent was obtained in each patient prior to participation.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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