NORMAL SPIROMETRY, GAS TRANSFER AND LUNG VOLUME VALUES IN PAPUA, INDONESIA

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Abstract. Spirometry is an efficient and clinically useful tool in the diagnosis and management of chronic lung disease. It relies on an appreciation of normal lung function that can vary between populations. In order to improve the utility of spirometry, gas transfer and lung volume measures for clinical and research use in Papua, Indonesia, we determined lung function in Papuan and non-Papuan Indonesian adults who did not have evidence of lung disease. A cross-sectional survey of Papuan and non-Papuan Indonesians 18 years or older with no history of chronic cough or recent wheeze was made. Spirometry, gas transfer and total lung capacity (TLC) were determined and regression models developed for normal values. The spirometry values were similar but not directly comparable to similar studies in Papua New Guinea populations. Papuan highland residents demonstrated independently greater values of gas transfer and total lung capacity in comparison to lowland Papuans. Values for lung function in apparent respiratory health were shown to differ between Papuan and non-Papuan Indonesian populations and in comparison to reference values derived from non-Indonesian populations. Differences in age-related decline in lung function would suggest that simple proportional correction based on values derived from non-Indonesian populations may be inappropriate and would support the development of similar reference values in other populations. Whether differences seen here are innate or occur as a consequence of in-utero and post-partum environmental exposure remains to be accurately elucidated.

INTRODUCTION

Spirometry is a tool that is ideally suited to the management of lung disease in a resource-limited environment. It is a relatively inexpensive, reliable and reproducible technique for assessing lung function that provides valuable information for the diagnosis and monitoring of lung disease. After purchase, resources required for ongoing maintenance and calibration are low and consumables for testing are minimal. Whilst the key to utilizing this tool is appropriate user training and instrument calibration it is also imperative, especially for diagnosis, that there is an appreciation of normal values for any given population. Whilst normal values for spirometry have been developed for residents of Papua New Guinea (Anderson *et al*, 1974) no similar validated resources are available for residents of Papua, Indonesia (formerly Irian Jaya).

Gas transfer and lung volume measures have more limited utility. Nevertheless in larger centers they can be a useful adjunct in the diagnosis of interstitial lung disease and chronic obstructive lung disease.

Significant differences in lung function in apparently healthy individuals exist among dif-

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ferent ethnic groups. These are likely to be related to a combination of innate genetic differences and environmental factors. In association with studies of lung injury in malaria and the long-term sequelae of tuberculosis we determined normal values for spirometry and gas transfer in residents of Papua Province, Indonesia who did not have evidence of lung disease.

MATERIALS AND METHODS

This was a cross-sectional study of normal adult lung function that was conducted at Mitra Masyarakat Hospital (RSMM) in Timika, Papua Province, Indonesia. This study occurred in association with concurrent studies of malaria-related lung injury and tuberculosis. Subjects were often family members accompanying those enrolled in these studies. Subjects were age ≥18 years and currently well with no history of current or recent wheeze (within the prvious 12 months), and no history indicative of chronic bronchitis (no cough productive of sputum on most days for ≥3 months per year for ≥ 2 years). Subjects were either indigenous Papuans or non-Papuan Indonesians. Papuans were further classified as usually resident in mountainous "highland" or coastal "lowland" areas. Pregnant women were excluded.

Assessment included questions relating to tobacco consumption, measurement of height and hemoglobin concentration (HemoCue, Dronfield, Derbyshire UK). Lung function measurement included spirometry, an assessment of total lung capacity (TLC), and a measurement of gas transfer (DL_{COSB}). Spirometry measures included: FEV_1, the volume expired in the first second of a forced expiratory manoeuvrer; FVC, the total volume expired; and FEV_1:FVC, the ratio of these two measures. Local medical staff employed by the project were trained in the supervision and quality assurance of lung function testing with on-going distant supervision of electronic test data by a respiratory physician.

Lung functions were measured using a pulmonary function testing station (TT544, Morgan Transflow System, Morgan Medical Ltd, Kent, UK) adapted for portable use. This allowed the equipment, which is usually only available in a respiratory function testing laboratory, to be portable and robust enough to allow transportation by air and road. It was possible to maintain and calibrate this equipment in isolated locations. Calibration involved twice-daily calibration of the flow detector and gas analysers using known gas mixture of helium (He), carbon monoxide (CO) and oxygen (O_2) concentrations.

Spirometry was performed using American Thoracic Society criteria for technique and reproducibility (American Thoracic Society, 1995). Values were converted to BTPS (body temperature, pressure, saturated with water vapor). Gas transfer and lung volumes were measured using the single breath technique (DL_{COSB}). This required subjects to breathe in a mixture of known concentrations and volumes of He, CO and O_2, hold their breath for 10 seconds, then exhale. The composition of the exhaled mixture was then analyzed. Gas transfer was included and taken as the greatest of two or more measurements if breath holding time was between nine and ten seconds and if the two highest measurements were within 10% of one another.

Data were analysed using Intercooled Stata 7.0 (Stata Corp, College Station, Texas, USA). Normal values for spirometry and gas transfer were derived using multivariate linear regression modelling and standard regression diagnostics. All statistical tests were two sided with a p-value of 0.05 taken to indicate statistical significance. Binomial 95% confidence intervals were calculated for dichotomous variables.

All research was conducted in accordance with national and institutional guidelines for human experimentation. The study was explained in the Indonesian language using local health providers and, where necessary, local language translators. Individuals who agreed to participate were provided with a written information sheet in Indonesian and signed a consent form. Approval to conduct the studies was granted by the ethics committee of the National Institute of Health Research and Development, Indonesian Ministry of Health and the Health Research Ethics Committee of Menzies School of Health Research and Northern Territory Department of Health and Community Services. Financial support was provided by a Wellcome Trust-National

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RESULTS

Descriptive data relating to subjects are presented in Table 1. There was a significantly greater proportion of women in the lowland Papuan group (χ^2, p<0.001) compared with highland subjects (χ^2, p<0.001) and non-Papuans (χ^2, p<0.001). Highland Papuans were shorter than non-Papuans (*t*-test, p<0.001). Hemoglobin were lower (ANOVA, p<0.01) in both highland (*t*-test, p<0.01) and lowland Papuans (*t*-test, p<0.01) compared with non-Papuans. Adequate spirometry was more often performed by non-Papuans (Fisher's exact test, p<0.01) in comparison with highland (Fisher's exact test, p<0.01) and lowland (Fisher's exact test, p<0.01) Papuans. There were no other significant differences among the groups for other descriptive data.

Linear regression modelling for FEV_1, FVC and FEV_1/FVC ratio is presented in Table 2 and for DL_{COSB}, DL_{COSB}/V_A and TLC in Table 3 with separate modelling for Papuan and non-Papuan Indonesians. Predicted FEV_1 and FVC for male and female Papuans is presented graphically in Fig 1. Although age was not a significant independent predictor of FVC in Papuans, and FEV_1 and FVC in non-Papuan Indonesians, it was included in the models due to its consistent association with spirometry variables in other populations. Height and gender, although just failing to reach statistical significance, were included in models of gas transfer and lung volume for

Table 1
Characteristics of subjects stratified by place of origin [BMI - body mass index (kg/m^2)].

		Papuan Indonesian		
	Non-Papuan Indonesian	Highland	Lowland	All
Number	53	75	32	107
Age [median yrs (IQR)]	28.7(25.6-33.2)	24.0(20.4-30.0)	28.7(24.0-36.2)	25.0(20.9-31.3)
Gender [% female (95% CI)]	25(14-38)	19(11-29)	69(50-84)	34(25-43)
Current smoker [% (95% CI)]	43(30-58)	36(25-48)	44(26-62)	38(29-48)
Height [mean cm (SD)]	161.2 (6.6)	157.3 (5.7)	158.7 (7.6)	157.7 (6.3)
Weight [median kg (IQR)]	60 (52-71)	58 (53-62)	56 (52-67)	58 (53-62)
BMI [median kg/m^2 (IQR)]	23.7(20.3-26.3)	23.1(22.0-24.7)	22.7(21.3-24.8)	23.0(21.6-24.7)
Hemoglobin at presentation [mean g/dl (SD)]	13.8 (1.6)	12.5 (2.4)	12.6 (2.3)	12.6 (2.3)
Spirometry adequate [% (95% CI)]	94(84-99)	75(63-84)	69(50-84)	73(63-81)
Gas transfer adequate [% (95% CI)]	71(57-83)	78(65-88)	73(54-88)	76(66-85)

Table 2
Regression modelling of spirometry variables for Papuan and non-Papuan Indonesians (all coefficients p<0.05 unless otherwise stated).

	Papuan			Non-Papuan Indonesian	
	FEV_1 (l)	FVC (l)	FEV_1/FVC ratio (%)	FEV_1 (l)	FVC (l)
Age (years)	-0.020	-0.010^{ns}	-0.4	-0.010^{ns}	-0.005^{ns}
Height (cm)	0.039	0.042	-	0.0413	0.043
Gender(male=0, female=1)	-0.551	-0.860	-	-0.575	-0.726
Constant	-2.558	-2.527	92.2	-3.114	-2.904
R^2	0.367	0.501	0.0857	0.537	0.567
MSE	0.574	0.561	9.8043	0.427	0.461

Table 3
Regression modelling of gas transfer and TLC for (a) Papuan and (b) non-Papuan Indonesians (all coefficients $p<0.05$ unless otherwise stated).

(a)

	Papuan		
	$DL_{CO}SB$(ml/min/mmHg)	$DL_{CO}SB/V_A$(ml/min/mmHg/l)	TLC (l)
Age (years)	-	-0.03	-
Height (cm)	0.29	-	0.05
Gender (male=0, female=1)	-4.29	-	-0.84
Hemoglobin (g/l)	1.05	0.19	-
Tobacco in last 24 hours (no=0, yes=1)	-2.82	-0.52	-
Location (lowland=0, highland=1)	3.33	-	0.45
Constant	-32.73	4.46	-3.80
R^2	0.59	0.39	0.57
MSE	4.58	0.76	0.62

(b)

	Non-Papuan Indonesian		
	$DL_{CO}SB$(ml/min/mmHg)	$DL_{CO}SB/V_A$(ml/min/mmHg/l)	TLC (l)
Age (years)	-0.36	-0.07	-
Height (cm)	$0.22^{p=0.05}$	-	$0.05^{p=0.05}$
Gender(male=0, female=1)	-7.56	$-0.59^{p=0.08}$	-0.65
Constant	6.99	8.37	-3.75
R^2	0.61	0.21	0.60
MSE	3.94	0.85	0.50

non-Papuan Indonesians as they improved the variance of these models considerably. Highland Papuans demonstrated a significant independent increase in gas transfer compared with lowland Papuans. This difference was also seen in the modelling of TLC and did not persist when controlling for alveolar volume (DL_{COSB}/V_A). Tobacco consumption, if present, was relatively uncommon with the median number of cigarettes smoked per day in current and past smokers of only 6 (IQR 4-12). This was not a significant predictive factor in the modelling of spirometry variables, though tobacco consumption within the last 24 hours was an independent predictor of gas transfer (DL_{COSB} and DL_{COSB}/V_A) in Papuan subjects and was incorporated.

DISCUSSION

We believe this is the first published study describing normal lung function in Papuan Indonesians. Normal spirometry data have been determined in mountain and island residents of Papua New Guinea (Anderson *et al*, 1974), a country that shares a land border with Papua, Indonesia. Normal values for spirometry are a valuable resource for the interpretation of lung function and the diagnosis and management of chronic lung disease and are presented graphically in Fig 1 for clinical use. The lack of a statistically significant association with age for FVC in Papuans, and FEV_1 and FVC in non-Papuan Indonesians, was surprising and may, at least, be partially attributed to the limited age distribution of the study sample. Daily tobacco consumption, if present, was at a relatively low level. Current and past tobacco smokers were included in the predictive equations of spirometry variables in light of the low level of exposure and the lack of an independent association between smoking and spirometry variables.

Predicted values for FEV_1 for Papuans and non-Papuans are compared to other populations in Fig 2 (Morris *et al*, 1971; Anderson *et al*, 1974;

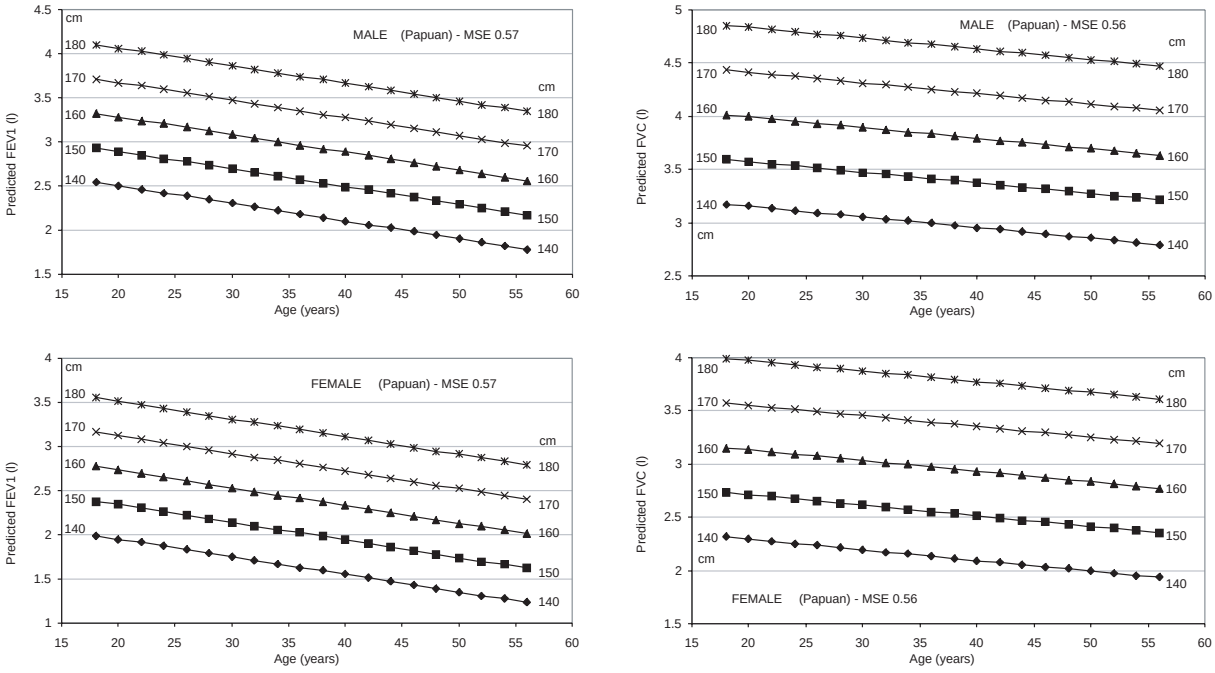

Fig 1–Predicted values for male and female Papuan Indonesians for FEV_1 and FVC for increasing age (years) and standing height (cm).

Patrick and Femi-Pearse, 1976; Maguire *et al*, 2000). Values for Papuans approximately paralleled those seen in Papua New Guinea coastal populations, though demonstrated a slightly lower rate of age-related decline. Predicted age-related decline in FEV_1 for non-Papuan Indonesians was even slower. Compared with African and indigenous Australian populations, Papuan and non-Papuan predicted values for FEV_1 were higher and closer to those predicted in Caucasian Americans. Whilst proportional correction of predicted values from other populations is commonly advocated, the difference in age-related decline demonstrated in this study would invalidate such an approach. This supports the need for the development and dissemination of predicted values such as these for normal spirometry in local populations, as has been undertaken in other countries in the region (Anderson *et al*, 1974; Ayub *et al*, 1987; Ismail and Zurkurnain, 1992; Pan *et al*, 1997).

The greater level of gas transfer seen in highland compared with lowland Papuans did not persist when controlling for lung size. A similar association with TLC indicates this association was due to greater lung size and potential surface area available for gas transfer for any given height in Papuan highlanders. Non-Papuan Indonesians demonstrated greater levels of gas transfer compared with Papuan and non-Indonesian values (Fig 3). Whether this represented a degree of selection bias in the sample surveyed or a consistent finding will require further study in a greater number of non-Papuan Indonesians.

Values of TLC in comparison with non-Indonesian populations (Fig 3) demonstrated lower predicted values for TLC for increasing height for lowland Papuans and non-Papuan Indonesians in comparison with values derived from American and indigenous Australian populations. This again reinforces the need for the development of local reference values, but as such testing is rarely used in clinical care in Papua currently, the need is less urgent.

A range of factors may explain differences noted between Papuan and non-Papuan Indo-

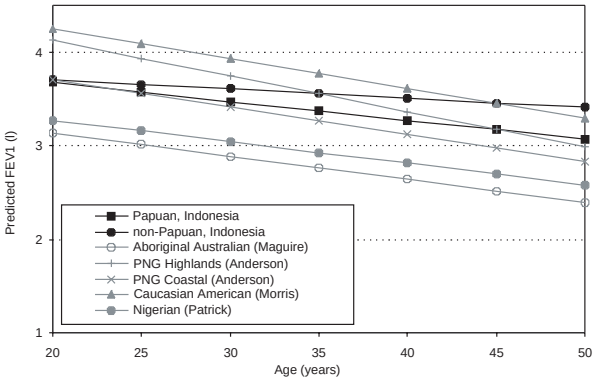

Fig 2–Comparison of Papuan and non-Papuan predicted FEV_1 with Aboriginal Australian (Maguire *et al*, 2000), Papua New Guinea (Anderson *et al*, 1974), American (Morris *et al*, 1971) and Nigerian (Patrick and Femi-Pearse, 1976) values for increasing age in a 170 cm tall male.

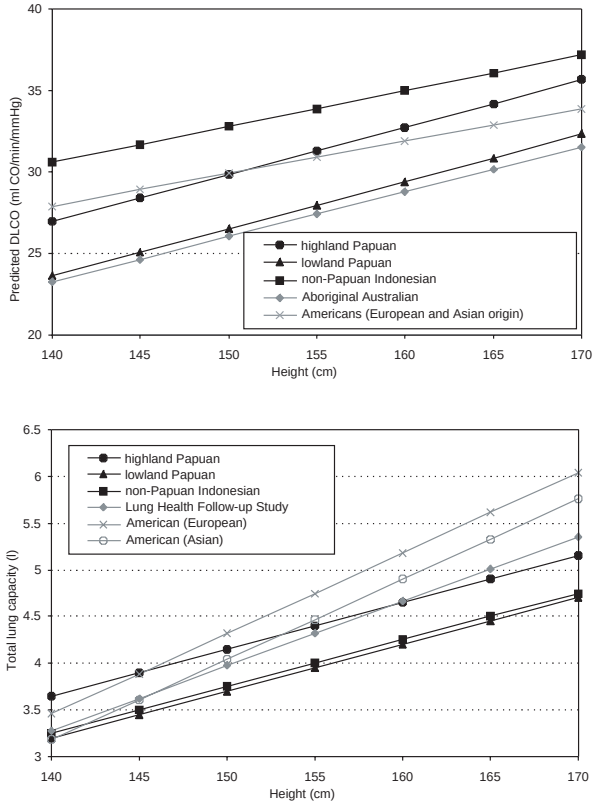

Fig 3–Comparison of Papuan and non-Papuan predicted $DL_{CO}SB$ and TLC with Aboriginal Australian (Maguire *et al*, 2002) and American (Korotzer *et al*, 2000) values for increasing height in a 20 year old, non-smoking male with a hemoglobin of 15 g/dl.

nesians in comparison with non-Indonesian populations. Methodological factors, including selection and measurement bias are possible. As Papuan controls were often family members of individuals with either malaria or tuberculosis, it is possible they were not representative of Papuans overall. Nevertheless the high rates of both these conditions in Papua make this unlikely. Non-Papuan Indonesians come from a broad range of locations in Indonesia. It is possible that innate and/or environmental exposures may be different in this group compared with the Indonesian population as a whole. The finding that the explained variance of the regression models (R^2) was higher for non-Papuan Indonesians would suggest that greater variability was not a factor here.

The other potential causes of the differences noted here are innate or environmental factors. Potential environmental factors include early environmental exposures, including intrauterine growth, growth in early post-partum life, respiratory infections, tobacco consumption and environmental pollution (including differences in housing and exposure to cooking/biomass fumes) as well as innate differences in thoracic volume and lung size. The contribution of these factors remain to be accurately elucidated though studies in other populations would indicate that these differences are unlikely to be due to innate population-specific differences alone. In other populations, being socially disadvantaged, poorer intrauterine and early post-partum growth, respiratory infections in early life and environmental pollution have all been shown to be associated with poorer lung function, including FEV_1 and TLC (Barker *et al*, 1991; Maguire *et al*, 2000, 2002). It is likely they are acting in a similar fashion in Indonesia. Fortunately all these are amenable to intervention, providing opportunities to optimise lung function and to prevent the development of chronic lung disease.

Spirometry is a useful and affordable tool in the diagnosis and management of chronic lung disease. Correct interpretation relies on an appreciation of what are normal values for any given population. The findings of this study provide a useful resource for clinicians and researchers working in Papua, Indonesia.

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