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Research Article

Relationships between Obesity, Cardiorespiratory Fitness, and Cardiovascular Function

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Background. Obesity and low cardiorespiratory fitness (CRF) have been shown to independently increase the risk of CVD mortality. The aim of this study was to investigate the relationship between CRF, body fatness and markers of arterial function. *Method and Results*. Obese (9 male, 18 female; BMI 35.3 ± 0.9 $kg \cdot m^{-2}$) and lean (8 male, 18 female; BMI 22.5 ± 0.3 $kg \cdot m^{-2}$) volunteers were assessed for body composition (DXA), cardiorespiratory fitness (predicted $\dot{V}O_2max$), blood pressure (BP), endothelial vasodilatator function (FMD), and arterial compliance (AC) (via radial artery tonometry). The obese group had more whole body fat and abdominal fat (43.5 ± 1.2% versus 27.2 ± 1.6%; $P < .001$ and 48.6 ± 0.9% versus 28.9 ± 1.8%; $P < .001$, resp.), and lower FMD (3.2 ± 0.4% versus 5.7 ± 0.7%; $P < .01$) than the lean subjects, but there was no difference in AC. AC in large arteries was positively associated with CRF ($R = 0.5$; $P < .01$) but not with fatness. *Conclusion*. These results indicate distinct influences of obesity and CRF on blood vessel health. FMD was impaired with obesity, which may contribute to arterial and metabolic dysfunction. Low CRF was associated with reduced elasticity in large arteries, which could result in augmentation of aortic afterload.

1. Introduction

Obesity and cardiorespiratory fitness (CRF) are independent predictors of cardiovascular (CV) and all-cause mortality [1–5]. Furthermore, it appears that CRF may be protective against the cardiovascular risk associated with obesity [6]. The mechanisms which mediate the relationships between obesity, CRF, and CV mortality risk are not entirely understood [5, 7]. However, given that the protective effects of CRF and the detrimental effects of obesity appear to influence CV mortality independently of other CV risk factors, it is of interest to investigate their influences on established markers of subclinical CV function. This will allow for a better understanding of the potential mechanisms by which obesity and CRF may influence the risk of CV mortality.

Increased adiposity, in particular visceral adiposity, is associated with reduced vascular endothelial function [8, 9]. Endothelial function refers to the general functional capacity of vascular endothelial cells, primarily mediated by their capacity to synthesize and release nitric oxide (NO) [10]. Reduced synthesis and/or availability of NO is associated with increased vascular permeability, inflammation, adhesion and thrombosis, and a reduced vasodilatory capacity, and abnormalities of endothelial function have been associated with a number of CV risk factors [11].

The noninvasive technique of measuring flow-mediated dilatation (FMD) in the brachial artery provides a marker of endothelium-mediated dilatory function. Previous studies have reported strong associations between FMD and risk of CVD [12–14]. Furthermore, a relatively low FMD has recently been identified as an independent risk factor for future CV events [15]. Both increased fatness and reduced CRF have been associated with lower FMD, and both weight loss and exercise training have been shown to improve FMD

in various populations [16–24]. In a study of apparently sedentary females, CRF was found to be more strongly associated with FMD than BMI; however, as CRF was expressed relative to total mass in this study, it was also partially a measure of obesity [16].

Decreased arterial compliance (elasticity) is an early indicator of increased CVD risk which may precede elevated BP and/or arterial stenosis [25]. Arterial compliance (AC) is reduced in subjects with, or at high risk of developing, arterial disease [26] and can be abnormal well before overt CVD develops [27]. Previous studies have found both decreased CRF [28] and increased adiposity [29] to be associated with reduced AC. Intervention studies have indicated that exercise training can improve compliance of the large capacitance arteries, either independently of or in association with improvements in CRF [30, 31]. It is not clear whether the protective effects of CRF in terms of reduced CV mortality risk might be in some way mediated by improvements in arterial compliance.

The aim of this study was to investigate the influence of obesity and CRF on arterial stiffness and function in a sedentary population in order to provide some insight into potential mechanisms by which obesity and CRF may mediate CV mortality risk. A sedentary population was chosen for this study to avoid the potentially confounding effect of exercise training and/or regular physical activity.

2. Method

2.1. Subjects. Twenty seven obese (BMI > 30 kg/m^2) and 26 lean (BMI 18–24.9 kg/m^2) sedentary male and female volunteers (40–65 years) were recruited from the general community in Adelaide, South Australia, using flyers and radio advertising. Initial screening for inclusion was conducted via written questionnaire and telephone interview. Applicants were excluded from participating if their BMI or age fell outside of the prescribed ranges, if they had a history of cardiovascular, metabolic, hepatic, or renal disease, were not sedentary (i.e., exercised > 1 time per week for the purpose of improving health), were taking blood pressure or cholesterol lowering medication, were smokers, or were pregnant or lactating. Written informed consent was obtained from all subjects prior to participation. The research was approved by the University of South Australia Human Research Ethics Committee.

2.2. Study Design. Participants were required to attend the research clinic on two occasions separated by not more than 1 week. Both visits were scheduled for the same time of day and subjects were required to attend each visit following an overnight fast (minimum 12 hours fasted). During the first visit, blood samples were collected for assessment of blood glucose, triglycerides and cholesterol after which blood pressure (BP), AC, and FMD were assessed. During the second visit, anthropometric, body composition, and CRF assessments were conducted.

2.3. Blood Analyses. Fasting blood (10 ml) was obtained by venepuncture. Plasma concentrations of glucose, triacylglycerols, and total cholesterol were measured on an automated centrifugal analyzer (Cobas-Bio, Rotkreuz, Switzerland) using standard commercial kits (Roche Diagnostica, Indianapolis, USA).

2.4. Cardiovascular Assessments. After participants had been lying supine for 10 min, BP and AC were measured using the HDI/Pulsewave CR-2000 Cardiovascular Profiler (Hypertension Diagnostics Inc, Eagan, MN). Recordings were made in triplicate at 5-min intervals. Endothelial function was assessed whilst supine by FMD as previously described by Raitakari and Celermajer [13, 32]. For FMD assessments, the diameter of the brachial artery was measured by a single operator using 2-dimensional B-mode ultrasound (LOGIQ 5; GE Medical Systems, Waukesha, WI). To induce reactive hyperaemia, a sphygmomanometer cuff was placed around the proximal region of the forearm (i.e., distal to the imaged brachial artery) and inflated to a suprasystolic pressure (200 mm Hg) for 5 min. Images of the artery were taken before cuff inflation, 10 s before cuff release, 10 s after cuff release, and then every 30 s for an additional 3 min. Arterial diameter was measured as the maximum perpendicular distance between the intima with the use of digital calipers (Logiq software, version 5 1.1X; GE Medical Systems).

2.5. Anthropometry and Body Composition. Each subject's height (Seca 220 stadiometer, Vogel & Halke, Germany) and weight (Ultimate Scale 2000, Tanita, Japan) were recorded to calculate BMI. Body composition was assessed by dual energy X-ray absorptiometry (DEXA) (Lunar Prodigy; General Electric, Madison, WI). During DEXA scans, subjects, wore a hospital gown and scans were performed in accordance with the manufacturer's instructions. Abdominal fat content was estimated from regional analysis of the DEXA scan by drawing a quadrilateral box with the base of the box touching the top of the iliac crest, the lateral borders extending to the edge of the abdominal soft tissue, and the upper margin touching the most inferior aspect of the ribs.

2.6. Cardiorespiratory Fitness. CRF was estimated using an incremental submaximal exercise test on a cycle ergometer (Egromedic 828E, Monark Exercise, Sweden). Subjects cycled for 5 mins at a cadence of 60 rpm at each of 3 incremental submaximal workloads. These workloads elicited a heart rate (HR) response equivalent to 50, 60, and 70 percent of age-predicted maximum, respectively, using the equation of Tanaka et al. [33] (200−(0.7*age[yr])). HR was recorded throughout each exercise test as 5 second averages using a personal HR monitor (Acurex Plus, Polar Electro, Finland). Oxygen uptake was monitored in 30 sec epochs during each workload by indirect calorimetry. Maximal oxygen uptake ($\dot{V}O_2$max) was estimated by extrapolating the linear regression plot of the$HR/\dot{V}O_2$ relationship to age-predicted maximum HR.

2.7. Physical Activity. All subjects completed a 3-day physical activity diary which included two week days and one weekend day in order to assess habitual activity levels [34].

Table 1: Comparative characteristics of lean and obese groups. Note: FFM - fat free mass; values represent mean ± SEM.

	Obese	Lean	*P*
Number (M/F)	9/18	8/18	—
Age (years)	49.6 ± 1.6	50.1 ± 1.3	.8
BMI ($kg \cdot m^{-2}$)	**35.3 ± 0.9**	**22.5 ± 0.3**	**<.001**
Body fat (%)	**43.5 ± 1.2**	**27.2 ± 1.6**	**<.001**
Abdominal body fat (%)	**48.6 ± 0.9**	**28.9 ± 1.8**	**<.001**
Total cholesterol ($mmol \cdot L^{-1}$)	6.7 ± 0.4	5.7 ± 0.3	.08
Glucose ($mmol \cdot L^{-1}$)	5.2 ± 0.2	5.3 ± 0.2	.31
Systolic BP (mmHg)	**127.0 ± 2.6**	**118.6 ± 3.1**	**<.05**
Diastolic BP (mmHg)	72.4 ± 2.0	67.0 ± 1.8	.06
Flow-mediated dilatation (%)	**3.2 ± 0.4**	**5.7 ± 0.7**	**<.01**
Arterial compliance ($ml \cdot mmHg^{-1} \cdot 10$)	16.5 ± 0.9	15.5 ± 0.6	.36
$\dot{V}O_2max$ ($L \cdot min^{-1}$)	**2.3 ± 0.2**	**1.8 ± 0.1**	**<.01**
$\dot{V}O_2max$ ($ml \cdot kg^{-1} \cdot min^{-1}$)	**23.0 ± 1.4**	**27.9 ± 1.1**	**<.01**
$\dot{V}O_2max$ ($ml \cdot kgFFM^{-1} \cdot min^{-1}$)	44.4 ± 1.7	42.0 ± 1.4	.28

2.8. Statistical Analysis. Statistical analysis was performed using SPSS (version 12, SPSS Inc, Chicago, IL, USA). Data were screened for normality of distribution using Shapiro-Wilk for separate groups and Kolmogorov-Smirnov for whole groups; data were accepted as normal where $P > .20$. Unpaired *t*-tests were used to compare means between the lean and obese groups. Analysis of variance was used to compare FMD measurements between groups, using the baseline arterial diameter as a covariate. Pearson's correlation coefficient was used to identify relationships between variables. Partial correlation analysis was used to adjust for additional variables where described. Statistical significance was set at an alpha level of 0.05. All data are shown as mean ± standard error of the mean (SEM).

3. Results

Subject characteristics are shown in Table 1. All variables were found to be normally distributed overall and when lean and obese groups were analysed independently. Age and gender was well matched between groups, and no difference was seen in physical activity diary results between groups (obese = 16 086 ± 650 kJ versus lean 16 321 ± 875 kJ). Body composition analysis confirmed the higher adiposity of the obese group in total (43.5 ± 1.2 versus 27.2 ± 1.6%) percentage body fat (%BF) and abdominal (48.6 ± 0.9 versus 28.9 ± 1.8%) percentage body fat (%ABF) compared to the lean group. Systolic BP was 8.4 mmHg greater in the obese group compared to lean. Mean FMD in the obese group was approximately half (56%) of that observed in the lean group. There were no differences in diastolic BP, HR, AC, plasma cholesterol, or glucose between groups. Absolute CRF ($L \cdot min^{-1}$) was significantly higher in the obese group compared with the lean, but when expressed relative to total mass ($ml \cdot kg^{-1} \cdot min^{-1}$), it was lower in the obese compared with lean. When expressed relative to fat-free mass, there was no difference in CRF between groups.

FMD was not related to CRF when expressed in either absolute or relative terms. AC was positively related to CRF expressed in either absolute terms or relative to total or lean mass (see Table 2). The relationships between AC and CRF were adjusted for all other CV risk factors measured (age, SBP, DBP, BMI, and TChol). This analysis did not change the relationship between AC and absolute CRF ($r = 0.61; P < .001$), or CRF relative to total mass ($r = 0.36; P = .02$) but eliminated the relationship with CRF relative to fat-free mass ($r = 0.26; P = .1$).

Correlation analysis was also performed on the obese and lean groups independently. The relationship between AC and CRF was stronger on all indices in the obese group compared to the whole group. Absolute CRF strengthened slightly $r = 0.72$ ($P < .001$); CRF relative to total mass increased to $r = 0.070$ ($P < .001$), and CRF relative to fat-free mass showed the greatest increase to $r = 0.07$ ($P < .001$). In the subanalysis of the lean group, the correlation between AC and absolute CRF weakened to $r = 0.41$ ($P = .05$), and there was no significant relationship when CRF was expressed relative to total or fat-free mass. There was no relationship between FMD and CRF when analysed separately for lean and obese groups.

SBP was significantly correlated with absolute CRF ($r = 0.31; P = .02$). Adjusting this analysis for the effect of FMD eliminated the relationship, or AC has no effect; however when adjusting for total mass, no relationship was present ($r = 0.12; P = .42$). Both SBP and CRF correlated with total mass ($r = 0.39; P = .006$ and $r = 0.70; P < .001$, resp.).

4. Discussion

Long-term prospective studies have found both CRF and obesity to be strong predictors of CV mortality [2–5]. Some evidence suggests that CRF may be a more influential moderator of CV risk than obesity because the influence of obesity is reduced or negated with high CRF [1, 4, 6]. However, other results have shown CRF and obesity to predict risk independently of each other [5]. In support of this independent effect, the results presented here suggest there is a differential mechanistic process involved with the

Table 2: Correlations between measures of fitness and arterial compliance for the total group, obese group, and lean group, and the partial correlation for the total group adjusted for systolic blood pressure (SBP), diastolic blood pressure (DBP), age, total cholesterol (total chol), fasting glucose, and body mass index (BMI).

Correlation with arterial compliance	r	P
Total group		
$\dot{V}O_2$max ($L \cdot min^{-1}$)	**0.64**	**<.001**
$\dot{V}O_2$max ($ml \cdot kg^{-1} \cdot min^{-1}$)	**0.39**	**.008**
$\dot{V}O_2$max ($ml \cdot kgFFM^{-1} \cdot min^{-1}$)	**0.49**	**.001**
Total group adjusted for SBP, DBP, age, total chol, fasting glucose, BMI		
$\dot{V}O_2$max ($L \cdot min^{-1}$)	**0.61**	**<.001**
$\dot{V}O_2$max ($ml \cdot kg^{-1} \cdot min^{-1}$)	**0.36**	**.02**
$\dot{V}O_2$max ($ml \cdot kgFFM^{-1} \cdot min^{-1}$)	0.26	.11
Obese group		
$\dot{V}O_2$max ($L \cdot min^{-1}$)	**0.72**	**<.001**
$\dot{V}O_2$max ($ml \cdot kg^{-1} \cdot min^{-1}$)	**0.70**	**<.001**
$\dot{V}O_2$max ($ml \cdot kgFFM^{-1} \cdot min^{-1}$)	**0.70**	**<.001**
Lean group		
$\dot{V}O_2$max ($L \cdot min^{-1}$)	**0.41**	**.05**
$\dot{V}O_2$max ($ml \cdot kg^{-1} \cdot min^{-1}$)	0.26	.21
$\dot{V}O_2$max ($ml \cdot kgFFM^{-1} \cdot min^{-1}$)	0.18	.40

protective effects of fitness as compared to carrying less fat. Further identification of these mechanisms may help to better inform therapeutic approaches to reduce CVD risk.

A previous cross-sectional study by Christou and associates [29] of the relationships between CRF, obesity, and CV risk factors in healthy adults found obesity to be associated with numerous CV risk factors including AC, assessed by aortic pulse wave velocity. However, CRF was only associated with metabolic markers of risk (triacylglycerols, fasting insulin, and insulin sensitivity). The effect of CRF is difficult to interpret in this particular study due to the inclusion of participants across a broad range of activity levels, thereby introducing potential confounding effects of physical activity habits [35]. This is particularly so due to the systematic inclusion of a highly endurance exercise-trained group. Lippincott and associates [16] found FMD to be significantly correlated with both obesity and CRF in a group of women with sedentary occupations. Whilst the physical activity associated with occupational demands was controlled for, a limitation of the study was the lack of control for other sources of physical activity. Therefore the present study is the first to directly compare markers of CV function between obese and lean individuals whilst controlling for the influence of habitual physical activity.

The results presented in this paper suggest a clear differentiation between the influences of obesity and CRF on CV function. FMD in the obese group was almost half that seen in the lean group, indicating an impairment in endothelial function in the obese group. While the mechanism underlying the relationship between endothelial dysfunction, and obesity is yet to be fully elucidated, evidence suggests multiple potential pathways [36]. Obesity is associated with alterations in production and secretion of lipids and lipoproteins and adipokines (increased leptin and resistin and decreased adiponectin) [37]. These changes can impact negatively on vascular endothelial function through increased proinflammatory pathways including increased endothelin-1, monocyte chemoattractant protein-1, pentraxin, tumor necrosis factor α, and interleukin 6 and 12 and through direct action on endothelial cells and vascular smooth muscle [37].

While FMD was reduced in obesity, it was not associated with CRF. This suggests that the cardioprotective effects of CRF may not be mediated via improved endothelial function. When considered in the context of previous findings of improvements in FMD with exercise training [38], this may suggest that these benefits are mediated through different mechanisms to those responsible for improvements in CRF. Because the population in the present study were sedentary the variance in CRF is due to underlying basal cardiorespiratory function not due to a training effect. Therefore, a limitation of this study is that the influence of higher CRF or increases in CRF due to exercise training on FMD cannot be predicted from these results. The correlation found by Lippincott and associates between CRF and FMD may have been biased by the influence of physical activity participation as discussed earlier. Furthermore, the effect of CRF in that study cannot be separated from the influence of obesity due to the expression of CRF relative to total mass. Only considering CRF in this manner incorporates a significant component of fat mass into the quantification of CRF.

The present study found no relationship between markers of obesity and AC, indicating that within a nondiseased, age-matched, and sedentary population, obesity does not negatively impact on AC. This is in contrast to the previously mentioned result of Christou and associates [31] who found that BMI and waist circumference were inversely associated with AC. This discrepancy may be due to the different methods of AC assessment (pulse wave velocity versus the Windkessel model of the CR-2000 in the present study), although good correlations have been previously reported between these two techniques [39]. Alternatively it may be due to methodological differences between the two studies including the inclusion by Christou et al. [29] of a range of BMI levels and physical activity/exercise training status as discussed previously. This is in contrast to the present study involving a direct comparison between an inactive obese and inactive lean sample. Irrespective of any underlying reasons, this apparent discrepancy warrants further investigation in follow-up studies.

CRF, when expressed as an absolute value ($L \cdot min^{-1}$ $\dot{V}O_2max$), was significantly higher in the obese group compared to lean. This is not entirely surprising as both groups were sedentary (untrained) and the obese group had higher fat-free mass as well as fat mass, indicating greater total muscle tissue and so greater maximal aerobic capacity [40]. When expressed in the more traditional method relative to total mass ($ml \cdot kg^{-1} \cdot min^{-1}$ $\dot{V}O_2max$), CRF was significantly lower in the obese group compared to lean. This again is not unexpected due to the large (and deliberate) discrepancy in total mass between groups. When expressed relative to lean mass ($ml \cdot kg^{-1}$ fat-free $mass \cdot min^{-1}$ $\dot{V}O_2max$), there was no significant difference in fitness between groups. Because the latter is a better indication of the relative oxidative capacity of the more metabolically active muscle tissue, it can be argued that this may be a more appropriate way to account for fitness when comparing a lean and obese population. It does not however account for the true functional capacity as the obese group have a larger mass to move for a given aerobic capacity. The strongest predictor of AC was absolute fitness, suggesting that a higher absolute oxidative capacity represents the greatest protection.

Whether expressed in absolute or relative terms, CRF was significantly related to AC, whereas AC was not related to markers of obesity and hence did not differ significantly between lean and obese subjects (i.e., no group effect). This implies that independently of obesity, AC is positively associated with CRF. Interestingly, when obese and lean groups were analysed separately, the correlations between AC and CRF increased in the obese group across all indices of CRF, particularly when expressed as total mass. Conversely, in the lean group it weakened the relation to absolute CRF and was no longer significant with CRF relative to total or lean mass. This suggests that despite there being no effect of obesity on AC, the influence of fitness on AC may be augmented by increased fatness.

Previous studies have shown that regular participation in endurance type exercise can result in improvements in AC [41], although it is unclear whether this is due to increased fitness or the chronic exposure to exercise, or a combination of both factors [35]. Further work is, therefore, required to determine the most appropriate exercise intervention for improving AC. As discussed above, this study sought to control for the influence of regular exercise exposure and, therefore, recruited only sedentary participants. This means that the results cannot be extended to the effects of regular exercise participation on CV function. Likewise, they cannot be interpreted to predict any modification in CV function as a result of interventions designed to modify either fatness or fitness. It should also be noted here that the fitness measures presented within this study were derived by way of submaximal testing and prediction of maximal capacity. Whilst this does somewhat compromise the reported values for CRF parameters, the interindividual and group comparisons remain valid.

Systolic blood pressure was slightly higher in the obese group compared to lean and it appears, due to the significant inverse correlations, that this may be primarily mediated via FMD and, to a lesser extent, AC. Although SBP was higher in the obese group, it was only greater by 7.6% and still clearly normotensive. By contrast, FMD was reduced in the obese group by 43.7% thus highlighting its value as a subclinical marker of vascular dysfunction. Interestingly there was a significant positive correlation between SBP and absolute CRF meaning that a higher fitness was associated with a higher resting SBP. Adjusting this analysis for either FMD or AC did not change this result. Adjusting for body mass however did negate this correlation suggesting that this relationship may be a consequential effect of body mass on both CRF and SBP. The influence of body mass on absolute CRF may be due to increased oxidative tissue mass as discussed above. However, the influence of body mass on SBP, given the lack of relationship between SBP and BMI or percentage body fat, remains an anomaly within these results.

While the design of the study allows for a well-controlled comparison of the effects of obesity and fitness on CV function, the limitations in study design must be considered when interpreting the results. Firstly, it must be acknowledged that due to the cross-sectional nature of the study, cause and effect cannot be concluded. These findings are an important contribution to the understanding of fitness and obesity on CV function, but further randomised controlled trials and cohort studies are required to demonstrate cause and effect. Secondly, by limiting the participants to lean (normal BMI), and obese it is not appropriate to draw conclusions across a broader spectrum of body mass index or tissue compositions.

In summary, this study demonstrated that in obesity FMD is substantially reduced. There was no impact of obesity on AC, indicating that obesity may not contribute to CV mortality through a loss of AC. CRF, however, was significantly associated with AC, indicating that the cardioprotective effects of a higher CRF may be related to maintenance of elasticity in central conduit arteries. Increased obesity through reduced endothelial function may augment the progression of arterial disease, thrombosis, and hypertension as well as, through decreased NO and muscle blood flow, metabolic dysfunction, leading to increased CV mortality risk. Reduced CRF with the associated decrease in AC may lead to increased cardiac afterload and, in turn, left

ventricular hypertrophy, reduced coronary perfusion, and increased CV mortality risk. Strategies aimed at reducing CV mortality must, therefore, aim to reduce adiposity in the obese and increase or maintain CRF in all people.

Conflict of Interests

No conflict of interests exists.

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