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Functional Exercise Capacity: It's Relation with Basal Nitric Oxide and Resting Cardiac Autonomic Activity in Young Healthy Individuals

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ABSTRACT
Background: Functional exercise capacity is a better predictor of adverse outcomes in cardiovascular disease (CVD) and healthy individuals as well. Mechanism of limitations in functional exercise capacity associated with CVD is not clear. Autonomic nervous system and local factors produced by the endothelium regulate the amount of blood flow to the different parts of the body. The aim of the study was to investigate if basal nitric oxide (NO) and resting cardiac autonomic activity determines the functional exercise capacity; and if basal NO is associated with the cardiac autonomic function in young healthy individuals.
Methods: A cross-sectional study was conducted on 58 young healthy subjects with normal BMI and age ranging between 18-35 years. Functional capacity was evaluated using a six-minute walk test (6MWD). Resting time domain and frequency domain components of heart rate variability; and basal total nitric oxide concentration (NOx) were estimated as index of cardiac autonomic function and endothelial function respectively.
Results: 6MWD was not significantly correlated with basal NOx (r=-0.138; p=0.302) and HRV indices: RMSSD (r=--0.004; p=0.975), pNN50 (r=0.114; p=0.394), LF (r=0.027; p=0.842) HF (r=0.001, p=0.996) LF/HF ratio (r= 0.094; p=0.482). There was a significant correlation between 6MWD and resting SBP (r=0.434; p=0.001), and PP (r=0.494; p<0.001). There was no significant relationship between basal NOx and HRV indices.
Conclusion: Functional exercise capacity was not significantly related with basal NOx and resting cardiac autonomic activity in young healthy individuals. Further, there was no interrelation between basal NOx and cardiac autonomic function. These findings suggest that basal NOx and resting cardiac autonomic function may not predict functional exercise capacity in young healthy individuals.

Keywords: Functional exercise capacity, endothelial function, nitric oxide, cardiac autonomic function

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INTRODUCTION

Functional exercise capacity (FEC) is a better predictor of adverse outcomes in cardiovascular disease (CVD)[1] and healthy individuals as well.[2-4] Functional capacity is reduced in individuals with CVDs. However, the mechanism of limitations in functional capacity associated with CVD is not clear. Individual's functional capacity depends on a complex integrated efforts and health of the pulmonary, cardiovascular, and skeletal muscle systems. Autonomic nervous system and local factors produced by the endothelium regulate the amount of blood flow to the different parts of the body. Among the several products of endothelium, a key molecule that maintains blood flow, vascular homoeostasis and integrity is nitric oxide (NO). It regulates vascular tone, vascular relaxation, vascular permeability and antithrombotic properties.[5,6] Sufficient bioavailability of NO is critical to normal endothelial function. Insufficient NO production/bioavailability, an hall mark of endothelial dysfunction is one of the central factor that is associated with all CVD including arterial stiffness, diabetes, hyperlipidemia and atherosclerosis.[6] Endothelial dysfunction with decreased NO bioavailability has been suggested as the early step in the development of CVD[7]. The reduction in NO bioavailability has been thought to be a factor that contributes for the limitations in functional capacity associated with CVD through inadequate coronary and peripheral blood supply.[8] However, a controversy exists on the relationship of NO or endothelial function with FEC.[9-16] Few studies have shown an association between endothelial function and exercise capacity [9-12] while others did not find any significant relation.[13-16] Studies have found an increase in NO level after physical exercise [9-11] and, shown a positive association between exercise performance and post-exercise NO level (exercise-induced NO production).[12] The association between basal NO and FEC is least studied, and we presume that basal NO may determine the functional capacity of an individual.

Autonomic nervous system (ANS) plays a central role in maintaining CV homoeostasis. Sympathetic and parasympathetic nervous system works together in coordination and regulates vascular tone, blood pressure and blood delivery to organs during different physiological conditions. But yet, the relation between resting cardiac autonomic function and functional capacity remains unclear. Cardiac autonomic imbalance contributes for hypertension and other CV diseases.[17] Further, cardiac autonomic dysfunction and endothelial dysfunction often co-exist in the development of various CV disease processes, suggesting that complex interactions may be involved between these two systems.[18] However, the mechanism of interrelation between endothelial function and cardiac autonomic function is not clear. Therefore, the aim of the study was to investigate if basal NO and resting cardiac autonomic activity determines the functional capacity; and if basal NO is associated with the cardiac autonomic function in young healthy individuals.

METHODOLOGY

Study design and population

A cross-sectional study was conducted on 58 young healthy subjects with 18.5-24.9 body mass index and age ranging between 18-35 years. Subjects with history of acute or chronic diseases, habit of smoking, chewing tobacco and consumption of beverages; subjects taking any medications, herbal drugs and vitamin supplements and subject refusal were excluded from the study.

Ethics

Written informed consent was obtained from participants for enrolment to the study. Prior approval of the study was taken from the institutional ethical committee of Sri B. M. Patil Medical College, Hospital and Research Centre, BLDE University, India as per the guidelines of Indian Council of Medical Research.

Method of collection of Data

All the recordings were done in the morning between 8 am to 11 am at room temperature following supine rest for 10 minutes.

a) Body mass index (BMI) was calculated using body mass divided by square of the body height and was expressed as kg/m^2.
b) Blood pressure (BP) and heart rate: Blood pressure was measured twice in a sitting posture using digital blood pressure monitor (Omron-HEM 7111). Pulse pressure (mmHg) was calculated as the difference between systolic and diastolic BP. Mean arterial Pressure (mmHg) was calculated by adding diastolic BP and $1/3^{rd}$ pulse pressure. Heart rate (beats per minute) was measured using digital BP monitor.
c) Functional exercise capacity: Functional capacity of an individual was evaluated using a six-minute walk test. Six-minute walk test (6MWT) is a simple, reliable and well-established tool to quantify the functional exercise capacity of an individual. In this test, the subject will walk as far as possible in six minute and the maximum distance walked will be recorded.[19]
d) Total Serum nitric oxide concentration: Total serum nitric oxide concentration (NOx) was estimated by Griess method using cadmium as a reducing agent for reduction of nitrate to nitrite.[20] To avoid the effect of physical activity on nitric oxide, subjects were given rest for 10 minutes before collection of blood sample. The subjects were also advised to abstain from foods such as cured meat, fish, cheese, herbal tea, beer and wine on the previous day to avoid dietary effect on serum nitric oxide concentration.[21]
e) Autonomic function test: Autonomic nervous system function was assessed by measuring heart rate variability (HRV). A short-term ECG for 5 minute was recorded in the standard limb lead II configuration using a four channel digital polygraph (Medicaid systems Pvt. Ltd, Chandigarh, India). Data free from ectopic beats and noise was included for further HRV analysis. Subjects were advised to breath normally during recording of ECG. The data acquired (R-R interval) was analyzed by time domain and frequency domain method using HRV analysis program developed by the Biomedical Signal Analysis Group, University Kuopio, Finland. Time domain indices included were root mean square standard deviation (RMSSD), successive normal to normal intervals that differ from each other by more than 50 ms (NN50), % of successive R-R intervals that differ by more than 50 ms (pNN50). Power spectral density of the R-R series was obtained by a non parametric fast furrier transform (FFT) technique. Total power in the frequency range (0-0.40Hz) was divided into very low frequency (VLF: 0-0.04), low frequency (LF: 0.04-0.15Hz) and high frequency (HF: 0.15-0.40Hz). LF (nu) measure reflects mainly sympathetic activity while HF (nu) reflects parasympathetic activity. LF/HF ratio reflects sympathovagal balance.[22,23]

Statistical analysis

Data obtained was expressed in mean and SD. Data was analyzed for normality. The association between the study variables was determined by using Pearson correlation coefficient or nor-parametric test on the basis of data distribution. Multiple linear regression analysis was done to find out the association between variables after the adjusting/controlling the confounders.

RESULTS

a) **Characteristics of participants:** Table 1 shows the characteristics of study sample. Mean age of the participants was 20.4 ±1.046 years. Equal numbers of male and female subjects were included in the study. There was no significant difference in age and BMI between male and female participants. As expected, there was a significant difference in SBP ($p<0.001$), PP ($p<0.001$), and MAP ($p=0.001$) between male and female subjects. Further, there was no significant difference in cardiac autonomic activity between males and females. Six-minute walking distance was more in males (539.38±71.72) when compared to females (470.23±50.18) and the difference was statistically significant. There was no gender difference in NOx and cardiac autonomic activity.
b) **Relationship between 6MWD and co-variables:** Table 2 shows correlation between 6MWT and co-variables: age, BMI, BP, HRV and basal NOx. Six-minute walking distance (6MWD) was not significantly correlated with basal NOx and HRV indices. Further, there was no significant gender difference in relation between basal NOx and 6MWT. Walking distance was significantly

correlated with SBP and PP. Further in regression analysis, SBP (β-0.969; $p<0.001$) was the significant predictor of functional capacity.

c) **Relationship between basal serum nitric oxide and cardiac autonomic function:** Table 3 shows the bivariate correlations between basal NOx and cardiac autonomic activity. There was no significant relationship between basal NOx and resting HRV indices.

DISCUSSION

The present study has investigated the role of basal NO and resting autonomic activity in determining functional capacity of an individual; and interrelations between the ANS activity and NO level as an index of endothelial function in young healthy subjects. Functional capacity was not significantly related with basal NOx and resting autonomic activity. Further, there was no significant correlation between basal NOx and cardiac autonomic function.

Endothelial NO plays an important role in maintenance of vascular integrity, and local regulation of coronary and peripheral blood flow.[5,6,8] Although, there is a controversy on the relation between endothelial function and exercise capacity, it has been speculated that impairment in NO function may contributes to limitations in functional exercise capacity associated with CVD through inadequate coronary and peripheral blood supply.[8] In the present study, we did not find any significant relation between basal NOx level and 6MWD, indicating that basal NO level does not predict the functional exercise capacity of an individual. Our findings were in accordance with other study findings.[13, 14,] Wang Y et al, investigated the relationship between endurance capacity (assessed by 1000 meter run) and endothelial function (assessed by measuring endothelial dependent flow-mediated vasodilation and circulating endothelial microparticles) in young healthy subjects. They did not find any association between endurance capacity and flow-mediated vasodilation, suggesting that endurance capacity may not depend on endothelial function in young adults.[13] Meeus M et al., also does not find any interrelation between NO concentration and physical activity level in patients with chronic fatigue syndrome and healthy individuals as well.[14] Jungersten L et al., have shown higher basal plasma nitrate in athletes when compared to non-athletes, suggesting that physical training may increase the NO formation.[11] They have also observed a significant positive association between exercise performance and post-exercise NO level in healthy subjects.[11] Similarly, other researchers have also demonstrated an increase in NO formation after mild/moderate physical exercise.[9-11] Contrarily, in another few studies, physical training did not significantly affect endothelial-dependent vasodilation function (that is NO-dependent) in healthy individuals, suggesting that there was no improvement in endothelial function.[13-16, 24] Even though, there is controversy on the effects of physical activity on endothelial function, the beneficial effects of physical training on cardiovascular health has been explained through an increased formation of NO by endothelial cells.[8, 10, 25, 26] We presume that NO formed during physical activity may remain high form short-term, favorably modulates cardiovascular system and resumes to normal level. Hence, post-exercise NO level may be associated to functional capacity, that (post-6MWT NO level) was not measured in the present study, which forms the limitation of the study. The findings from our study and others suggests that basal NO level may not predict the functional capacity in healthy individuals.

As state above, ANS plays a central role in cardiovascular homoeostasis and, regulates vascular tone and blood flow to the organs during both rest and work. In the present study, functional capacity was not significantly interrelated with resting HRV indices such as RMSSD, NN50, LF (nu), HF (nu) and LF/HF ratio, suggesting that resting cardiac autonomic function does not predict functional capacity of a healthy individual. Oliveira SR et al., systematically reviewed eighteen observational studies those assessed the association of cardiac autonomic function and physical fitness. They found a weak and inconclusive evidence for the association between physical work and frequency domain indices such as LF (nu/ms^2), HF (nu/ms^2) and LF/HF ratio, which are in accordance with our study findings in healthy individuals.[27] In another study, Hautala AJ et al., reported an association between basal HF (ms^2) component of power spectrum of HRV (an index of parasympathetic activity) and the physical training response in terms of aerobic power. Higher the basal parasympathetic tone (HF) better was the response to exercise, suggesting that resting cardiac autonomic function is associated with improvement in exercise capacity in sedentary healthy individual.[28]

Available evidences shows that cardiac autonomic dysfunction and endothelial dysfunction often co-exist in the pathogenesis of CV disease, indicating that these two systems may be inter-linked.[17] Both the systems are involved in central and local regulation of cardiovascular system. Sympathetic activation has been shown to attenuate endothelial function.[29, 30] Another study have shown that sympathetic activation results in decrease in endothelial-dependent flow-mediated vasodilation (FMD) in elderly individuals and attenuation of this sympathetic activity restores the endothelial-dependent FMD.[30] Sverrisdottir YB et al., have measured the muscle nerve sympathetic activity and reactive hyperemic index (index of endothelial function) in healthy individuals. They found a reciprocal relation between sympathetic activity and endothelial function. Further, they also showed that physical activity was positively associated with endothelial function and negatively associated with sympathetic nerve activity.[31] These studies have reported an inverse relation between sympathetic nervous system activity and endothelial function, but the mechanism of association is not yet understood. Evidence from the animal studies indicates that factors those amplify NO function may promote inhibition of sympathetic activity and facilitation of vagal activity.[32, 33] Contrarily, in the present study there was no significant interrelation between NOx and HRV indices, suggesting that endothelial NO may not be the direct factor that links the association between endothelial function and cardiac autonomic function in healthy individuals. Other possible linking pathways should be investigated to explore the mechanism of association between endothelial and cardiac autonomic function.

CONCLUSION

Functional exercise capacity was not significantly related with basal NOx and resting cardiac autonomic activity in young healthy individuals. Further, there was no interrelation between basal NOx and cardiac autonomic function. These findings suggest that basal NOx and resting cardiac autonomic function may not predict functional exercise capacity in young healthy individuals. Endothelial and cardiac autonomic function may be interrelated but NO is not the direct linking factor. The possible existence of an interrelation between functional capacity, NO and autonomic activity should be investigated in further studies in middle-aged/elderly individuals and patients with CVD as-well to explore the underlying mechanism of limitations in functional exercise capacity.

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Table 1: Characteristics of study participants

Variables	Total (n=58) Mean ± SD	Males (n=29) Mean ± SD	Females (n=29) Mean ± SD	p-value
Age (years)	20.4 ±1.046	20.76 ± 1.12	20.1 ± 0.9	0.017*
BMI (Kg/m²)	22.02±1.99	22.25 ± 2.28	21.75 ± 1.75	0.352
SBP (mmHg)	116.02±11.81	123.93 ± 9.25	109.17 ± 9.58	<0.001***
DBP (mmHg)	75.53±7.04	78.84 ± 6.53	74.0 ± 6.98	0.15
PP (mmHg)	40.48±8.23	45.48 ± 7.9	35.17 ± 5.39	<0.001***
MAP (mmHg)	89.03±8.04	93.58±6.61	85.79±6.67	0.001***
HR (bpm)	96.39±11.53	75.69±13.33	77.58±9.4	0.534
LF (nu)	72.56±9.31	72.09±11.03	72.35±6.91	0.916
HF (nu)	78.45±12.82	27.86±11.0	31.78±18.71	0.336
LFHF ratio	3.0±1.16	3.03±1.24	2.835±0.94	0.512
6MWD	507.8±71.13	539.38±71.72	470.23±50.18	<0.001***
NO (mMol/L)	37.85±16.83	36.38±16.49	39.27±16.34	0.505

*p<0.05, **p<0.01, ***p<0.001

Table 2: Bivariate correlations between 6-minute walking-distance and co-variables (n=58)

Co-Variables	**6 Minute Walking Distance (meters)** Total (n=58)		Males (n=29)		Females (n=29)	
	r-value	p-value	r-value	p-value	r-value	p-value
Age (years)	0.18	0.178	0.105	0.589	-0.056	0.772
BMI (Kg/m²)	-0.077	0.564	-0.250	0.191	-0.030	0.879
SBP (mmHg)	0.434	0.001***	0.289	0.128	0.013	0.946
DBP (mmHg)	0.0152	0.256	0.031	0.875	0.140	0.468
PP (mmHg)	0.494	0.001***	0.313	0.098	0.205	0.285
MAP (mmHg)	0.299	0.22	0.156	0.420	-0.082	0.672
HR	-0.141	0.292	-0.072	0.710	-0.340	0.071
RMSSD	-0.004	0.975	0.100	0.607	0.180	0.350
NN50	0.079	0.555	0.123	0.523	0.0.16	0.936
pNN50	0.114	0.394	0.202	0.294	0.084	0.667
Total Power	-0.065	0.626	0.018	0.925	0.322	0.089

LF (nu)	0.027	0.842	-0.126	0.515	-0.030	0.878
HF (nu)	0.001	0.996	0.123	0.524	0.226	0.236
LF/HF ratio	0.094	0.482	-0.082	0.672	0.170	0.377
NO (mMol/L)	-0.138	0.302	0.028	0.885	0.140	0.470

*p<0.05, **p<0.01, ***p<0.001

Table 3: Bivariate correlations between basal nitric oxide concentration and cardiac autonomic function (n=58)

HRV indices	NO (mMol/L)) Total (n=58)		Males (n=29)		Females (n=29)	
	r-value	p-value	r-value	p-value	r-value	p-value
RMSSD	-0.103	0.444	0.125	0.519	-0.018	0.926
NN50	0.076	0.569	0.161	0.404	0.225	0.240
pNN50	0.014	0.919	0.143	0.459	0.024	0.901
Total Power	-0.147	0.272	0.056	0.771	-0.140	0.469
LF (nu)	0.099	0.460	0.177	0.359	0.044	0.820
HF (nu)	-0.12	0.368	-0.177	0.359	-0.177	0.371
LF/HF ratio	0.042	0.753	0.166	0.388	0.013	0.948

*p<0.05, **p<0.01, ***p<0.001

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