

BRACHIAL ARTERY DIMENSIONS, FLOW-MEDIATED REACTIVITY, AND
PHYSICAL FUNCTION IN OLDER ADULTS

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Abstract

Human aging is associated with deterioration in physical functional ability. The causes are complex and multifactorial, but are presumed to include the presence and extent of cardiovascular disease. **Purpose:** To examine the associations between brachial artery (BA) dimensions, flow-mediated dilation (BAFMD) and physical function in 28 older adults (age: 84.6 ± 10.9 , range 66 to 98 yrs). **Methods:** High-resolution ultrasonography was used to measure BA diameters at rest and following 5min of forearm occlusion. Physical function was assessed using the Continuous Scale-Physical Function Performance (CS-PFP) test. **Results:** Pearson correlation revealed that BAFMD ($r = -.39$), and all physical function parameters of the CS-PFP declined with age at an alpha of $p = .04$ and $p < .01$, respectively (UBS, $r = -.69$; UBF, $r = -.78$; LBS, $r = -.77$; BALCOR, $r = -.74$; END, $r = -.81$; PFP total score, $r = -.79$). Six-minute walk scores (a component of the CS-PFP) also declined with age ($r = -.72$, $p < 0.01$). Mean BA resting diameter and BAFMD were 4.31 ± 0.77 mm and $1.89 \pm 1.99\%$, respectively. Resting diameter was inversely associated with BAFMD ($r = -.45$, $p = .02$). Partial correlation (controlling for BMI) was used to account for the influence of participant size on vascular and physical function measures. The results indicated an association between BAFMD and several CS-PFP sub-scales with an alpha of $p < .05$ (END, $r = .40$; UBF, $r = .39$; LBS, $r = .39$; BALCOR, $r = .38$). CS-PFP total score ($r = .38$) and UBS ($r = .28$) were associated with BAFMD at alpha of $p = .06$ and $p = .18$, respectively. Notably, the difference between resting and peak diameters, as a group, was not significant for the study sample. Two participants in the study sample had $\text{BAFMD} > 5\%$, thus the sample was biased towards “non-responders.” **Conclusion:** These results appear to confirm predicted trends for

physical function decline and reduced vasoreactivity in older adults. Uniquely, this study is the first to suggest a link between BA reactivity and age-appropriate measures of physical functional status. Therefore, BAFMD could potentially provide information regarding the impact of CVD and vasoreactivity on the functional characteristics of the population.

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Chapter 1. Introduction

Brachial artery dimensions and flow-mediated dilation are associated with severity and progression of occlusive cardiovascular disease (CVD) and numerous CVD risk factors including advancing age (Allen, Wilson, Tulley, Lefevre, & Welsch, 2000; Celermajer et al., 1994; Gerhard, Roddy, Creager, & Creager, 1996; Herrington et al., 2001; Kool et al., 1995; Laurent et al., 1996; Lekakis et al., 1998; Ravikumar, Deepa, Shanthirani, & Mohan, 2002; Sorenson et al., 1994; Steinberg et al., 1997; Taddei et al., 1995; Tawakol, Omland, Gerhard, Wu, & Creager, 1997). Consequently, non-invasive brachial analyses have been proposed as a useful approach for describing CVD risk in large population-based studies (Herrington et al.). While it is becoming increasingly clear that brachial dimensions and reactivity are of use in quantifying the presence and severity of disease, it is also reasonable to suggest that these measures may provide information about impairment of the cardiovascular system and the impact of CVD and other associated risk factors on the functional characteristics of the population.

In the context of the “Disablement Pathway,” (Figure 1.1) Verbrugge and Jette (1994) suggest that disablement begins with some pathology, injury, or congenital condition that may lead to impairment in the function of various physiologic systems (e.g. cardiovascular). This impairment may, in turn, lead to functional limitations (i.e., problems in executing activities of daily living [ADLs]) potentially resulting in a gap between a person’s capabilities and the demands of the environment (i.e., disablement).

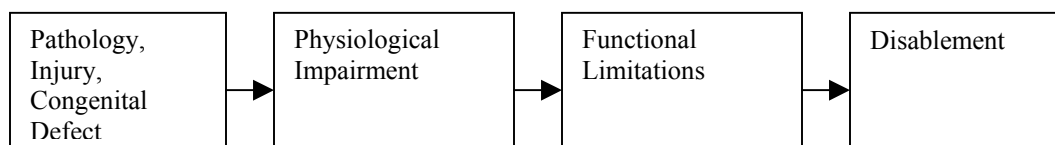


Figure 1.1 The Disablement Pathway

Thus, the link from disease to disability will benefit from an examination of impairments and functional limitations that may accompany the disease process. The purpose of this study was to examine the association among age, brachial artery dimensions and reactivity, and physical function in older adults. Evidence of an association in this regard extends the usefulness of brachial artery analysis to include not only information about the presence and severity of CVD and associated risk factors, but the **impact** of such pathology on the functional characteristics of the population.

Although function is somewhat ambiguous and subject to cultural and secular biases, tests of physical function in older adults can provide pertinent information regarding an individual's ability to live independently (Rikli & Jones, 1997). A test of physical function is the Continuous Scale-Physical Functional Performance test (CS-PFP; Cress et al., 1996) that requires individuals to perform ADLs in a standardized fashion, such as carrying groceries, climbing a flight of stairs, and sweeping debris from the floor into a dustpan. The CS-PFP has high test-retest reliability ($r=0.84-0.97$) and has been validated against other traditional measures of physical fitness in relatively functional older adults, and with health-related quality of life as measured with the SF-36 (Cress et al.). Furthermore, the CS-PFP discriminates between independent-living older adults and those with dependent-care needs (Cress et al. 1996, 2003).

To present, no published data have addressed the question as to the association between brachial artery analyses and physical function; however, the available evidence suggests that vascular dimensions and reactivity are correlated with age, and that brachial artery flow-mediated dilation (BAFMD) is associated with physical activity patterns and physiologic capacity in older adults. Studies have shown that older men with a history of

regular endurance training and thus, higher VO_{2max} also have higher levels of endothelium-dependent dilation (Jensen-Urstad, Bouvier, & Jensen-Urstad, 1999; Rinder, Spina, & Ehsani, 2000; Rywik et al., 1999). Therefore, we hypothesized that age would be directly associated with brachial artery (BA) diameter and inversely associated with BAFMD and physical function (Celermajer et al., 1994; Gerhard et al., 1996; Herrington et al., 2001; Shephard et al., 1997). We also hypothesized that resting BA diameter would be inversely associated with BAFMD and physical function (Anderson et al., 1995; Celermajer et al.; Herrington et al.). Lastly, we hypothesized that BAFMD would be directly associated with physical functional ability in older adults (Jensen-Urstad et al.; Rinder et al.; Rywik et al.).

Chapter 2. Methods

Participants. Twenty-eight older adults (ages 66-98) responded to an invitation to participate, and subsequently provided informed consent to participate in the study. The sampling procedure involved a random selection of older adults residing within a 40-mile radius of Baton Rouge, LA. The 2000 voters registration and US 2000 census reports were cross referenced and used as the list of potential participants. The ages of the volunteers were verified by birth certificate. The exclusion criteria were persons scoring less than 25 on the Mini Mental State Exam (MMSE) and those persons in American Heart Association Class D (i.e., symptoms of cardiovascular and/or metabolic disease at rest).

Procedures. Participants reported to the testing facility at 7:00am on the day of testing. Following the completion of informed consent and medical history information, vascular ultrasonography imaging was conducted at approximately 8:30am. At approximately 2:00pm on the same day, the participant performed the CS-PFP. The procedures for these tests are described below.

Vascular Measures. BAFMD testing was conducted at the Pennington Biomedical Research Center. Brachial artery assessments were obtained using high-resolution ultrasound (Toshiba Powervision SSA-380A with a 7.5-MHz linear array transducer) prior to, during, and following 5-minutes of forearm occlusion. Prior to the experiment, subjects were instructed to fast and refrain from exercise for 12hrs and alcohol for 48hrs. Baseline ultrasound images were obtained following 15-minutes of supine rest in the longitudinal view, approximately four centimeters proximal to the olecranon process, in the anterior/medial plane.

With the image depth initially at four centimeters, gain settings were adjusted to provide an optimal view of the anterior and posterior walls of the artery. Once settings were optimized, they were kept constant throughout the experiment. All imaging was performed on the non-dominant arm with the subject in the supine position and forearm extended and slightly supinated. Forearm occlusion consisted of inflation of a blood pressure cuff, positioned approximately one centimeter distal to the olecranon process, to 240mmHg for 5-minutes. Brachial artery images were recorded on CD and super-VHS videotape for 30sec at baseline, and continuously from the final 30sec of occlusion until 5-minutes post-release. Throughout the brachial imaging procedure blood pressures were measured in the contra-lateral arm in order to account for any variation in central cardiovascular responses to the testing protocol.

Images were analyzed using specialized imaging software (Brachial Analyses Tool). Arterial diameters (mm) were calculated as the mean distance between the anterior and posterior wall at the vessel-blood interface. BAFMD was calculated as the percent difference between the peak diameter observed following occlusion and the resting diameter.

The resolution of the brachial image in the current study allowed for a caliper accuracy of 0.028mm. The reproducibility of this technique in our laboratory has yielded average mean differences in brachial artery diameter change for days, testers, and readers of 1.91%, 1.40%, and 0.21mm respectively, with intra-class correlation coefficients of 0.92, 0.94, and 0.90, respectively (Welsch et al., 2002)

Physical Function. In following the HEF schedule, physical function testing was conducted approximately 5 hours after the vascular imaging at the Pennington

Biomedical Research Center. Physical function was assessed using the Reduced Continuous Scale – Physical Function Performance Test (CS-PFP). This test battery was first validated in 1996 (Cress et al.). It includes several tasks that require the participant to perform ADLs (i.e., carrying a pot from the sink to a stove, emptying a washer, walking a flight of stairs, sweeping a floor, etc.) in a standardized fashion. The tests are either time to completion scores, and/or weight carried, height reached, etc. Moreover, the tests are grouped according to “low-effort,” “medium-effort,” and “high-effort.” Participants were encouraged to complete the tests both quickly and safely. For greater detail please see Cress et al. (1996). As noted above, the investigators have recently examined the test-retest reliability and inter-tester reliability, and observed intraclass correlation coefficients to be in the range of 0.87-0.95.

Statistical Analysis. The associations among all study variables were examined using Pearson correlation. Partial correlation, controlling for BMI, was used to examine the associations between vascular and physical function measures. Values were expressed as the mean±SD. T-tests were also used to measure the statistical significance of the difference between peak and resting BA diameters.

Chapter 3. Results

Descriptive statistics of the subject population are provided in Table 3.1. The study population included 15 males and 13 females. The participants did not have any overt symptoms of CVD and none scored less than 25 on the MMSE. Additionally, there were no adverse events during testing.

Bivariate analysis was initially employed to evaluate the associations among all study variables and revealed correlations among age, anthropometric, vascular, and physical function measures. See Table 3.2 for a description of the correlation coefficients.

Table 3.1 Participant Descriptives

n=28	Mean±SD	Minimum	Maximum
Age (yrs)	84.6±10.9	66.0	98.0
Weight (kg)	73.1±18.3	39.1	128.2
Height (cm)	163.90±11.98	142.2	184.6
BMI	26.9±4.5	17.47	41.29
Waist-Hip	0.92±0.10	0.76	1.15
Systolic Pressure (mmHg)	137.4±19.2	100.0	170.0
Diastolic Pressure (mmHg)	76.3±11.3	50.0	100.0
Resting BA Diameter (mm)	4.31±0.77	2.74	5.54
Peak BA Diameter (mm)	4.39±0.75	2.97	5.60
BAFMD (%)	1.89±1.99	-0.92	8.39
CS-PFP Total	40.18±23.38	3.88	81.39

Pearson correlation did not reveal an association between resting BA diameter and age as hypothesized; however, an inverse association was observed between age and BAFMD. Additionally, there was an apparent age-association among all physical function parameters of the CS-PFP (i.e. UBS, UBF, LBS, BALCOR, END, PFP total, six-minute walk). In regard to vascular and physical measures, resting BA diameter appeared to be inversely associated with BAFMD, and all physical function parameters of the CS-PFP, except for UBS, were associated with BAFMD with an alpha of $p < 0.10$ in all cases.

In order to account for the influence of participant size on the vascular and physical function measures, partial correlation was utilized to analyze the association between vascular and physical measures. When controlling for the variables of height, weight, and BMI, partial correlation revealed slightly improved correlation coefficients. For example, results of the correlation analyses, when controlling for BMI, summarized in Table 3.3, revealed direct associations between BAFMD and the CS-PFP parameters of UBF, LBS, BALCOR, and END at $p < 0.05$ and associations with UBS and CS-PFP total score of $p = .18$ and $p = .06$, respectively.

Table 3.2. Pearson Correlation Coefficients

	Age	Weight	BMI	Rest diam	Peak diam	BAFMD	PFPP total	UBS	UBF	LBS	BALCOR	END	6min walk	dyspnea
Age	-	-.47*	-.35	.14	.11	-.39*	-.79*	-.69*	-.78*	-.77*	-.74*	-.81*	-.72*	-.09
Weight		-	.81*	.57*	.59*	.006	.51*	.57*	.27	.51*	.48*	.50*	.48*	.04
BMI			-	.40*	.41*	-.06	.31	.29	.29	.27	.29	.31	.32	.10
Rest diam				-	1.0*	-.45*	.12	.24	-.15	.15	.11	.09	.15	.25
Peak diam					-	-.37	.16	.27	-.12	.19	.15	.13	.17	.27
BAFMD						-	.34	.25	.36†	.35†	.35†	.36†	.12	.09
PFPP total							-	.94*	.83*	.99*	.96*	1.0*	.95*	.21
UBS								-	.72*	.97*	.83*	.91*	.88*	.20
UBF									-	.79*	.77*	.83*	.76*	.19
LBS										-	.92*	.97*	.93*	.24
BALCOR											-	.98*	.90*	.16
END												-	.94*	.20
6min walk													-	.18
dyspnea														-

Abbreviations: BMI, body mass index; BAFMD, brachial artery flow-mediated dilation; PFPP total, CS-PFPP total score; UBS, upper body strength score; UBF, upper body flexibility score; LBS, lower body strength score; BALCOR, balance and coordination score; END, endurance score.

*Significant correlation $p < .05$; † $p < .10$

Table 3.3 Partial Correlation Coefficients (Controlling for BMI)

	Rest diam	Peak diam	BAFMD	PFP total	UBS	UBF	LBS	BALCOR	END
Rest diam	-	.99	-.46	-.02	.13	-.32	.04	-.02	-.05
Peak diam		-	-.37	.03	.17	-.28	.09	.03	-.006
BAFMD			-	.38†	.28	.39*	.39*	.38*	.40*
PFP total				-	.93*	.81*	.99*	.96*	1.0*
UBS					-	.70*	.96*	.81*	.90*
UBF						-	.77*	.74*	.81*
LBS							-	.91*	.97*
BALCOR								-	.97*
END									-

*Significant Correlation $p < .05$; † $p < .10$

Chapter 4. Discussion

The objective of this study was to examine relationships among age, BA dimensions and reactivity, and physical function among a population of older adults. The study population consisted of 15 males and 13 females between the ages of 66 to 98 years old. None of the participants were contraindicated for exercise testing and no adverse events were reported in response to the study protocol.

The data from the present study are consistent with the appearance of age-related changes in vascular parameters and physical function. The BA resting diameters and reactivity of the study sample were similar to those reported by Herrington et al. (2001) for a similar age range. In contrast to Herrington et al., the present findings did not reveal an association between age and resting BA diameter as hypothesized. Previous studies have shown that BA diameter gradually increases with advancing age (Celermajer et al., 1994; Herrington et al.). A possible explanation for the lack of an association between age and resting BA diameter in the present study is that the age range of the subjects was from 66 to 98 years. Careful examination of Herrington's research reveals an increase in resting BA diameter with age up to approximately 65 years, after which, the change in diameter appears to plateau. The age-associated increase in resting BA diameter may have been masked in the present study by the fact that 19 out of the 28 individuals were over the age of 80 years. However, when comparing the present data to previous work in our laboratory, mean BA diameters in the study sample are considerably larger than those observed in younger populations. An explanation for the increase in diameter with age is currently not fully understood; however, several mechanisms including structural and neural changes have been suggested. A common compensation to the development of

atherosclerotic disease is enlargement of large conduit arteries in an attempt to preserve luminal area (Labropoulos et al., 1998). In addition, as peripheral resistance in arteriolar beds increases with age, larger conduit vessels expand similar to the swelling observed in a garden hose when clamped at one end (Lakatta & Levy, 2003).

Given the lack of association between age and baseline diameter, it is quite intriguing that there was an association between BAFMD and age. The observation of the age-related decline in BAFMD may indicate a reduction in the mechanisms contributing to dilation as opposed to merely detecting the influence of structural qualities of the vessel on flow-mediated dilation. The mechanisms for a lower BAFMD with advancing age are not entirely understood, but are thought to involve neural, humoral, local, and structural components. The traditional belief is that a reduction in BAFMD is a reflection of endothelial dysfunction involving the production or reaction to endothelial-derived factors such as nitric oxide and prostaglandins. However, it is now recognized that BAFMD is very much influenced by many other vascular controls. For example, the size of the vessel is a strong predictor of the reactivity of the vessel such that a larger vessel tends to react less (Anderson et al., 1995; Celermajer et al., 1994; Herrington et al., 2001). This finding is again confirmed in the present study where there is an inverse association between BA resting diameter and reactivity. More than likely, the changes in BAFMD with advancing age reflect a change in several controllers and their interaction rather than one specific mechanism. The current study is not adequate in terms of pinpointing the precise factors involved in the loss of reactivity, but does go beyond the traditional belief of endothelial dysfunction. Changes in autonomic control associated with aging may also play a role in the observed decline in vascular function. Alpha- and

beta-adrenergic receptor number and sensitivity decrease with advancing age, and therefore the amount of catecholamines needed for vasodilation and constriction of various vascular beds increases. Finally, the increased stiffness of the smooth muscle surrounding the artery due to age-related increased collagen, decreased elastin, and increased sodium levels may also influence the reactivity of the vasculature (Celermajer et al.; Lakatta & Levy, 2003).

With regard to physical function, the findings of the present study are also consistent with previous research (Aniansson et al., 1988; Quetelet, 1835; Shephard et al., 1991). Our results indicate that there is approximately a 1.4% decline in physical function with advancing age. These findings are consistent with the previously reported range for age-related loss in function. The classic study by Quetelet found a 1.6% loss per year in handgrip strength by the age of 65 years. More recent studies have shown a decline of 0.8% per year by 80 to 90 years and a loss of 6% to 8% per decade between the ages of 45 to 75 years (Aniansson et al.; Shephard et al.).

The main purpose of this study was to examine the extent to which brachial artery analyses are associated with physical function characteristics in older adults. We hypothesized that BA diameter would be inversely associated with physical function, and that BAFMD would be directly correlated with physical function. Although resting BA diameter was not associated with physical function, a direct association was observed between BAFMD and physical function parameters of the CS-PFP. This finding is unique in that no other studies to date have examined the specific association between BAFMD and physical function in older adults; however, the proposed link seems logical. One would expect an individual needs an adequate cardiovascular system to contribute to

good physical function. In fact, previous studies have documented that a high exercise capacity is directly associated with endothelium-dependent dilation in older adults (DeSouza et al., 2000; Jensen-Urstad et al., 1999; Rinder et al., 2000; Rywik et al., 1999). The significant correlation between BAFMD and the END domain of the CS-PFP further suggests the importance of an adequate circulatory system. Although the studies by Rinder et al., Rywik et al., Jensen-Urstad et al., and DeSouza et al. examined BAFMD in athletic and sedentary populations with regard to high levels of physical activity, the observed correlation between exercise capacity and BAFMD appears to be somewhat similar with regard to physical function in older adults. Interestingly, however, BAFMD was also associated with several other CS-PFP parameters that are, on face value, not cardiovascular dependent (i.e. UBF, UBS, BALCOR). Thus, the question comes to mind concerning the nature of the association between BAFMD and physical function. What are the mechanisms responsible for such an association? Many of the age-related physiological changes over time, such as decreased blood and stroke volumes, decreased capillary to fiber ratio, decreased motor units, and decreased fat free mass, result in inadequate perfusion of tissue. This decrease in nutritive flow to tendons and muscles over time compromises the health of that tissue and ultimately leads to losses in flexibility, strength, and balance and coordination.

Inasmuch as physical function is complex and multifactorial, the findings of the present study must be interpreted cautiously. As a group, differences between the peak and resting BA diameters were not significant, therefore the vasodilatory response to the 5-minutes of occlusion was not significant. Moreover, previous findings by our laboratory suggest that individuals with a BAFMD less than 3% may be considered as

“non-responders,” whereas, those above 5% are clear “responders.” Our results indicate that 21 participants had a “vasodilatory” response less than 3%, whereas only two participants had vasodilation greater than 5%. In this context, the present study was heavily weighted towards “non-responders.” As the data set grows, a wider range of responses will allow for more confident interpretation of the findings.

According to Verbrugge and Jette’s (1994) model of disablement, if a pathology or impairment can be identified, interventions can therefore be utilized in an attempt to attenuate physical limitations and disablement. Interestingly, vascular dimensions and vasoreactivity provide valuable information regarding the cardiovascular-risk of the general population and may arguably serve as a measure of “impairment,” and thereby provide insights concerning the physical functional limitations of older adults. Although the study sample may be referred to as potential “non-responders,” the present data did reveal an association between BAFMD and aspects of functional performance on the CS-PFP in the study sample of older adults. To more fully appreciate the potential relationship between vasoreactivity and physical function and to more clearly understand how this association fits into the disablement model, a larger study sample with a broader range of vasodilatory responses is needed. Nonetheless, the data appear to be moving in a direction that supports the use of BAFMD as a measure of not only global health status and vascular reactivity, but also for providing a greater link towards understanding the association between vascular disease and physical function. Thus, BA dimensions and reactivity should be included in the healthy aging index as one measure of the successful aging of older adults. Such an index would allow for early interventions in the

disablement model for those at greatest risk for disease and disablement in an attempt to promote optimal physical and mental health of the aging population.

Similar to the decline in vascular measures associated with age, the loss in physical function is complex and multifactorial. In addition to the observed association between vascular reactivity and physical function, there are other physiological changes that occur with advancing age and likely account for a significant percentage of the decline in physical function. For example, the decrease in muscle mass and the lowering of action potential thresholds result in the loss of strength and power. Moreover, stiffness of connective tissues and joints increases with aging thereby causing decreased joint stability and mobility. Also, concurrent with advancing age is a decrease in blood and plasma volumes, and a subsequent decrease in venous return and stroke volume in the older adult. These are only a few of the many physiologic variables that potentially impact physical function in the aging adult. Other mechanisms responsible for functional decline may include external factors such as cognitive function, depressive symptoms, and social support systems (Cress et al., 1995). The influence of decreased levels of physical activity and disuse could also explain the significant declines in physical function with aging (Rikli & Jones, 1997).

One of the limitations of our study was the complexity of imaging the vascular data. The Brachial Analyses Tool software is complex and only semi-automated. Due to structural changes and increased prevalence of scar tissue with advancing age, the overall image quality was not the best. Although we controlled for non-sinus beats and excluded them from the data analysis, the possible impact of such arrhythmias on stroke volume and thus vascular function cannot be determined. Moreover, the cross-sectional nature of our

data only allowed us to observe an association between brachial artery dimensions, flow-mediated dilation, and physical function.

Longitudinal studies are needed to further understand the role of metabolic and arterial changes that may occur with time, and their impact on vasoreactivity and physical function. Moreover, future studies should look to identify possible thresholds of BAFMD with regard to pathology and physical function. More specifically, is there a threshold of BAFMD whereby a further decrease in vasoreactivity suggests an increased risk for CVD, and is there also a threshold for BAFMD that indicates an increased risk for loss of physical function? Future studies should also examine whether or not these potential thresholds of BAFMD correspond to the previously established thresholds for declines in physical function such as a CS-PFP score less than 57 (Cress & Meyer, 2003). Exercise intervention studies are also necessary to determine if improvements in BA reactivity and physical functional ability are simultaneous.

Chapter 5. Conclusion

The present data lend support for the existence of several important associations. While, the present data do not confirm a direct association between resting BA diameter and age, they confirm an inverse association between age and BAFMD. Further, resting BA diameter was inversely associated with BAFMD. Uniquely, there was a direct association between BAFMD and physical function among the population of older adults tested. These findings suggest that vasoreactivity may play a role in the complex nature of physical function.

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