Age-Related Changes in Inferior Vena Cava Dimensions among Children and Adolescents with Syncope

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Objective To test the hypothesis that increased venous compliance manifested as inferior vena cava (IVC) dilation is an important substrate for syncope in children.

Study design IVC diameters were measured in 191 children and adolescents with syncope and in 95 controls. Subjects were divided based on age <12 years (younger group) and ≥12 years (older group). IVC measurements at the right atrial junction (IVC-RA), 10 mm below the IVC-RA junction (IVC-RA10), and at the point of maximal diameter (IVCmax) were made. The linear relation to body surface area (BSA) was confirmed, as were dimensions indexed to BSA (iIVC). Relationships between iIVC and the time of day were evaluated.

Results In the syncope group, the mean age was 12.9 ± 3.6 years, mean weight was 54.7 ± 23 kg, and mean BSA was 1.5 ± 0.4 m^2. Among controls, all IVC dimensions varied linearly with BSA ($P < .001$). In the older group (140 patients with syncope and 60 controls), all iIVC dimensions were larger in the syncope cohort: iIVC-RA, 9 vs 7.7 mm/m^2 ($P < .0001$); iIVC-RA10, 9.4 vs 8.1 mm/m^2 ($P < .0001$); iIVCmax, 11.7 vs 10.6 mm/m^2 ($P = .002$). In the younger group (51 patients with syncope and 35 controls), there were no differences in iIVC measurements between the syncope cohort and controls: iIVC-RA, 10.2 vs 11.3 mm/m^2; iIVC-RA10, 11.7 vs 12.0 mm/m^2; iIVCmax, 14.2 vs 14.7 mm/m^2 ($P > .05$ for all).

Conclusions The IVC is enlarged in teenagers with syncope compared with controls, suggesting that venous capacitance and resultant pooling play roles in the pathogenesis of syncope. In contrast, younger children with syncope do not demonstrate IVC dilation, suggesting that their syncope arises from a different mechanism. *(J Pediatr 2019;207:49-53).*

Syncope, defined as a sudden loss of consciousness with complete neurologic recovery, has a cumulative incidence of 35% by age 18 years and 50% by age 21 years.[1] Although the final common pathway is global cerebral hypoperfusion, various mechanisms may provoke it, including decreased cardiac output from increased vagal tone, decreased arterial tone, vasodilatation, and orthostasis.[2,3] Increased venous compliance has been postulated as the pathophysiology of syncope in young adults,[4,5] with orthostatic venous pooling leading to paradoxical activation of the cardioneural inhibitory reflexes.[6] The fall in cardiac output is a consequence of diminishing stroke volume due to reduced venous return from blood pooling in the lower venous and splanchnic systems secondary to impaired splanchnic vasoconstriction.[3,7]

A study in young adult subjects has shown larger diameters of the inferior vena cava (IVC) in those with vasovagal syncope compared with controls, and the authors suggested that increased venous compliance manifests as IVC dilation, which in turn results in exaggerated abdominal venous pooling during standing, with resultant orthostatic symptoms.[8] Decreased abdominal venous tone may be a contributing factor in some patients with reflex and vasovagal syncope.

Although isolated dilatation of the IVC in the absence of structural heart disease has been reported[9,10] and subsequently evaluated in young adults,[11] whether the IVC is dilated in children and adolescents with syncope is unknown. We hypothesized that IVC dilation without volume overload, pericardial disease, or right heart disease may be a marker of decreased abdominal/lower limb venous tone and venous compliance in children and adolescents.

Methods

A retrospective review of 213 children and adolescents who underwent echocardiographic evaluation for syncope between January 2016 and December 2017 was performed. Subjects with congenital heart disease, acquired heart disease,

BSA	Body surface area
iIVC	Indexed inferior vena cava
IVC	Inferior vena cava
IVCmax	Maximal diameter of the inferior vena cava
IVC-RA	Inferior vena cava-right atrial junction

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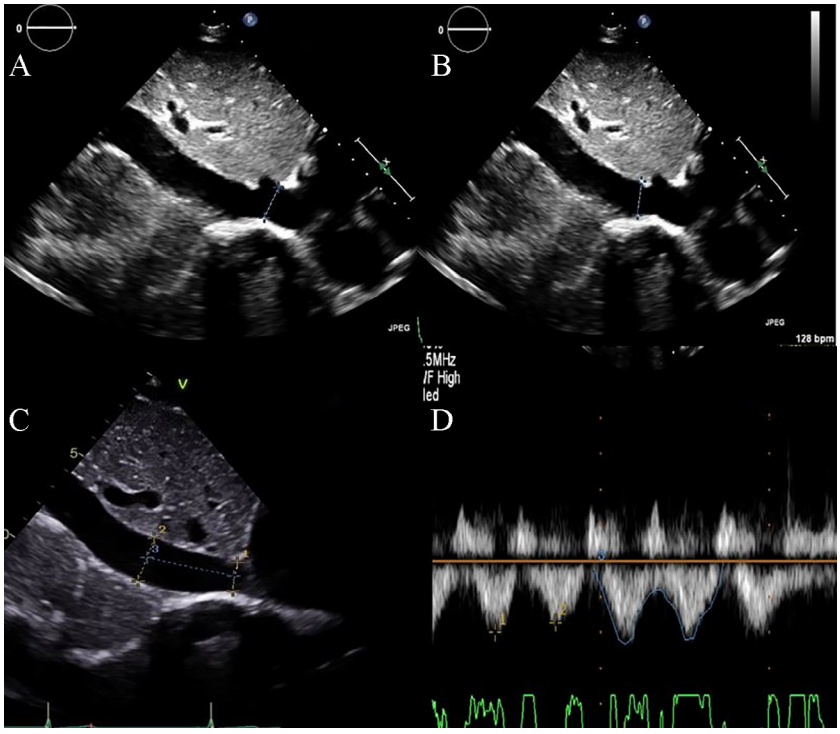

Figure 1. Measurements of the IVC in subcostal sagittal views. **A,** IVC measured at the IVC-RA. **B,** IVC measured at IVC-RA10. **C,** IVCmax and distance of IVCmax from the IVC-RA. **D,** IVC systolic and diastolic velocities.

hypertension, systemic noncardiac disease, cardiac arrhythmias, right heart dilatation, greater than physiological tricuspid regurgitation, or flow reversal in the IVC or hepatic veins were excluded from the study. Demographic data were collected, including time and date of the study, sex, age, height, weight, race, heart rate, and blood pressure. Body surface area (BSA) was calculated.[12] The University of Arkansas for Medical Science Institutional Review Board approved this study, and appropriate interinstitutional data transfer agreements were in place.

All the patients with syncope were age- and sex-matched with a control cohort. The control cohort was obtained from a prospectively collected database from the University of Nebraska Medical Center and Children's Hospital and Medical Center, Omaha, for a previously published study of normative data on systemic venous diameters.[13]

Echocardiographic studies were performed with the patient in a nonsedated state in a supine position using a commercially available ultrasound system (Phillips iE33; Philips, Andover, Massachusetts or GE Vivid E95, GE Healthcare, Milwaukee, Wisconsin). All images were stored in an echocardiography PACS storage and review system (Syngo Dynamics, Siemens, Germany). All IVC measurements were performed offline, as shown in **Figure 1**.

The long-axis image of IVC was obtained from the subxiphoid window. The IVC was measured proximal to the hepatic vein insertion, at the IVC-right atrial junction (IVC-RA), as recommended by the American Society of Echocardiography guidelines for performance of pediatric echocardiography[14] (**Figure 1**, A). The IVC in the long axis was also measured 10 mm below the IVC-RA (IVC-RA10) as recommended in adult guidelines[15] (**Figure 1**, B). The maximal IVC diameter (IVCmax) was also obtained, and the distance from the IVCmax to IVC-RA was measured (**Figure 1**, C). An IVC Doppler was obtained with a sample volume of 10 mm within the vein, proximal to the entry of the hepatic vein (**Figure 1**, D). Maximal systolic and diastolic velocities and mean velocities were recorded. All measurements were made in triplicate and averaged.

Tricuspid regurgitation was evaluated based on the width of the regurgitant jet in the apical 4-chamber view. Right ventricular volume and function assessed qualitatively and recorded in the echocardiogram reports were noted.

The linear relations of IVC measures to BSA were confirmed in the control group using linear regression. IVC dimensions were then indexed to BSA (iIVC). Continuous variables were compared using the Student *t* test, and binary variables were compared using the χ^2 test. Potential relations between iIVC and the time of day at which the echocardiogram was recorded were examined using linear and nonlinear (Holliday model) regression in both the control and syncopal groups. *Z*-scores for normalized IVC measurements were derived from means and SD values established in the age-matched control groups.

To assess intraobserver and interobserver agreement, IVC measurements were repeated in 15 randomly chosen subjects by the primary observer and a second blinded observer. Bland-Altman plots were derived to identify possible bias (mean divergence) and the limits of agreement (2 SDs of the divergence).

Table I. Characteristics of the study population

Characteristics	Syncope group (n = 191)	Controls (n = 95)	*P* value
Sex, female/male, n	96/95	37/58	.084
Age, y, mean ± SD	12.9 ± 3.62	12.16 ± 4.59	.190
BSA, m^2, mean ± SD	1.5 ± 0.4	1.447 ± 0.5	.163
Height, cm, mean ± SD	156.6 ± 21	152.2 ± 24.6	.133
Weight, kg, mean ± SD	54.7 ± 23	50.9 ± 24.5	.211

Intraclass correlation coefficients were calculated for testing measurement variability. Statistical analyses were performed using commercially available software (Minitab version 16.1; Minitab, State College, Pennsylvania).

Results

Of 213 subjects with syncope who otherwise met our inclusion criteria, 22 were excluded because of incomplete echocardiographic data, yielding a syncope cohort of 191 children and adolescents. The series also included 95 age- and sex-matched controls. Patient demographic data are presented in **Table I**. There were no significant differences between the syncope and control groups in sex, age, height, weight, or BSA.

Subjects (both the syncope and control groups) were divided into subgroups based on age <12 years (younger group) and >12 years (older group). The syncope cohort had 140 older subjects and 51 younger subjects, who were compared with 60 older and 35 younger controls (**Tables II** and **III**).

All IVC measures varied linearly with BSA in both the control and syncope groups ($P < .001$ for all regressions; **Figure 2**; available at www.jpeds.com). All IVC dimensions were greater in the older syncope cohort compared with their age- and sex-matched controls: iIVC-RA, 9 vs 7.7 mm/m^2 ($P < .0001$); iIVC-RA10, 9.4 vs 8.1 mm/m^2 ($P < .0001$); iIVCmax, 11.7 vs 10.6 mm/m^2 ($P = .002$). The younger syncope cohort showed no significant difference in iIVC measurements compared with controls. Among controls, no linear or nonlinear associations of significance were identified between any of the iIVC measurements and time of day (**Figure 3**; available at www.jpeds.com). In the syncopal cohort, although iIVC-RA and iIVCmax did not vary throughout the day, iIVC-RA10 peaked significantly between 1 p.m. and 2 p.m. Bland-Altman analysis showed good intraobserver and interobserver agreement for measurements (**Figure 4**; available at www.jpeds.com). For all measurements, the intraclass correlations showed very good agreement, with the coefficients slightly higher for intraobserver comparisons (**Table IV**; available at www.jpeds.com).

Discussion

Syncope is a common clinical problem that occurs across a broad age spectrum. The mean age of the initial presentation of pediatric syncope is 12-13 years.[4] In one study that included subjects with a wide age range, the first syncopal episode occurred at 0-81 years in a skewed distribution, with a mode of 13 years, a median of 18 years (IQR, 12- 37 years), and a mean of 26 ± 20 years.[16,17] A study of young adults (mean age, 23 years) with vasovagal syncope revealed dilated IVC in the absence of right heart disease.[11] The adult literature contains sporadic case reports of idiopathic dilatation of the IVC with vasovagal syncope.[10]

Our hypothesis is in accordance with studies conducted in young adults that showed relative increases in splanchnic blood volume during the tilt test in patients with syncope.[6] Other studies have demonstrated that abdominal compression is more effective than lower extremity compression in preventing orthostatic symptoms and have suggested that abdominal venous blood pooling plays a role in pathogenesis of this type of syncope.[8] Our findings lend further support to the concept that in adolescents with syncope, IVC enlargement may serve as a surrogate clinical marker of elevated systemic venous compliance, which contributes to their tendency to faint. On the other hand, no significant difference in IVC diameter was found between children with syncope aged <12 years and normal controls, which suggests that the mechanism of syncope might not be venous pooling in this age group.

In normal individuals, upright posture results in a gravity-mediated downward displacement of 300-800 mL of blood to the vasculature of the abdomen and lower extremities.[18] This causes a 40% decrease in stroke volume and a subsequent drop in arterial pressure. These changes are dynamic in nature and are influenced by such factors as vascular compliance, intravascular volume, and muscular activity.[18] Previous investigations of patients with syncope have found decreased stroke volume and cardiac output during the head-up tilt test.[2,19]

Venous occlusion plethysmography has demonstrated greater blood volume pooling in the lower half of the body in women with orthostatic symptoms compared with normal controls.[9] Mobilization of peripheral venous blood to the central circulation is adversely affected, resulting in a drop in stroke volume in those experiencing syncopal symptoms.[6,7] Venous hypotension, not decreased arterial blood pressure, is considered the primary physiological event in advance of the drop in cardiac output. This is likely why patients with vasovagal syncope tend to have normal blood pressure despite the presence of orthostatic symptoms.[5]

Table II. IVC dimensions and *z*-scores in the younger group

Dimensions	Younger syncope cohort (n = 51)	*Z*-score (relative to matched controls)	Matched controls (n = 35)	*P* value
iIVC-RA, mm/m^2	10.2 ± 2.86	−0.41 + 1.06	11.32 ± 2.7	.079
iIVC-RA10, mm/m^2	11.7 ± 2.53	−0.32 + 1.13	12.02 ± 2.23	.474
iIVCmax, mm/m^2	14.23 ± 0.4	−0.44 + 0.16	14.67 ± 2.5	.309
Distance from IVCmax to IVC-RA, cm	2.9 ± 0.8	−0.28 + 0.26	3.18 ± 3.1	.492

IVC diameters have a linear relation to BSA, but the slope of that relation is not 1, and the intercept is not 0. Therefore, IVC diameter normalized to BSA is not constant over BSA and is smaller as BSA increases.

Table III. IVC dimensions and *z*-scores in the older group

Dimensions	Older syncope cohort (n = 140)	*Z*-score (relative to matched controls)	Matched controls (n = 60)	*P* value
iIVC-RA, mm/m^2	9.04 ± 2.82	+1.12 + 2.27	7.65 ± 1.24	<.001
iIVC-RA10, mm/m^2	9.4 ± 2.94	+0.87 + 1.97	8.1 ± 1.49	<.001
iIVCmax, mm/m^2	11.7 ± 3.39	+0.60 + 1.84	10.6 ± 1.84	.002
Distance from IVCmax to IVC-RA, cm	2.27 ± 1.78	−0.27 + 1.71	2.77 ± 1.04	.015

IVC diameters have a linear relation to BSA, but the slope of that relation is not 1, and the intercept is not 0. Therefore, IVC diameter normalized to BSA is not constant over BSA and is smaller as BSA increases.

Our findings indicate that the pathophysiology of syncope in children and young adults differs with age. Older children and young adults may have more vasodilatation, leading to progressive hypotension in later phases of syncope. Children aged <12 years tend to not have IVC dilatation in association with syncope, so their pathophysiology likely differs from that seen in older children and adults. In a study examining the etiology of syncope in children aged 0-6 years, acute pain and subsequent loss of consciousness was the most common clinical scenario (approximately 43% of cases); 13.5% of the children had vestibular-mediated syncope, and 8% lost consciousness due to dehydration from gastroenteritis.[20] Our present findings suggest that children aged >12 years generally share the high venous capacitance pathophysiology identified in adults with syncope.

These data suggest the potential role of age-based targeted therapy for syncope in young people. Midodrine is a prodrug whose active metabolite is an agonist of the peripheral alpha-1 adrenergic receptor. It causes both venoconstriction and arteriolar constriction, thereby increasing cardiac output and increasing peripheral resistance.[21] Numerous clinical trials in adults and children have shown that midodrine alleviates syncopal symptoms by 60%-70% in symptomatic patients.[22] Based on our observations, we speculate that this therapy might prove less effective for younger children, in whom the pathogenesis of syncope is likely not high venous capacitance. Going forward, a prospective study is needed to measure IVC measures in different positions (supine vs standing), as well as the changes in IVC dimensions either after prolonged standing or during the tilt table test. Serial IVC measurements may be helpful in monitoring response to therapy.

The present study is subject to the limitations inherent a retrospective study design. The indication for the echocardiographic examinations was syncope, which may be a broad term for a referring physician, so whether all patients had actually lost consciousness cannot be established with certainty. Some may have been merely presyncopal. The study's retrospective design complicates interpretation of the data, given the lack of objective controls for hydration status, physical fitness, or race. These factors are all at least potential confounders. There also was no accounting for the timing of echocardiography relative to either the syncopal event or to any diurnal IVC diameter variation. The respiratory cycle was not recorded during echocardiography, so any IVC dimensions that might include a change in IVC diameter with respiration could not be evaluated. The group of younger patients and their matched controls was smaller than the group of older patients; nonetheless, a post hoc power analysis indicated that the magnitude of change noted in the older group likely still would be detected in the younger group.

In conclusion, the larger IVC diameter in adolescents with syncope compared with controls suggests that venous capacitance and resultant venous pooling play roles in the pathogenesis of syncope in these patients. In contrast, younger children with syncope do not demonstrate IVC dilation, which suggests that their syncope arises from a different mechanism. The presence of dilated IVC in children and teens with syncope may potentially have therapeutic implications. ■

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50 Years Ago in *The Journal of Pediatrics*

Thiamine-Responsive Megaloblastic Anemia

Rogers LE, Porter FS, Sidbury JB. J Pediatr 1969;74:494-504

In 1969, Rogers et al described an 11-year-old girl with bilateral sensorineural hearing loss and diabetes mellitus who presented with recurrent megaloblastic anemia responding only to thiamine supplementation, an astute observation discovered through meticulous clinical observation and extensively planned laboratory evaluations. This was the first time that thiamine had been implicated in hematopoiesis. Although not definitively linked in the original article, the constellation of thiamine-responsive megaloblastic anemia, sensorineural deafness, and diabetes mellitus went on to be known as "thiamine-responsive megaloblastic anemia syndrome" or Rogers syndrome.

Forty years after the original publication, geneticists localized the cause of thiamine-responsive megaloblastic anemia syndrome to chromosome 1q23.2-23.3, specifically the *SLC19A2* gene,[1] via studies of 4 unrelated families with this clinical phenotype. *SLC19A2* was subsequently confirmed to encode a high-affinity thiamine transporter protein.[2] Interestingly, a "single enzyme defect" was the hypothesis postulated by the authors in the originally described case.

The genotype–phenotype correlation was confirmed using mouse models in which the *SLC19A2* mutation proved to be associated with development of hearing loss, diabetes, and megaloblastic anemia, which improved with thiamine supplementation.[3] These studies also helped to suggest a role for the thiamine pathway in development of other types of hearing loss and diabetes, research that is currently ongoing.

Although the disease is now well-characterized, the only available treatment option remains high-dose thiamine supplementation. Furthermore, similar to Rogers' case, patients often show improvement only in their megaloblastic anemia without improvement in hearing loss or diabetes. However, with the disease-driving mutation now identified, in the setting of rapidly expanding molecular therapy techniques, improved treatment strategies are certainly forthcoming.

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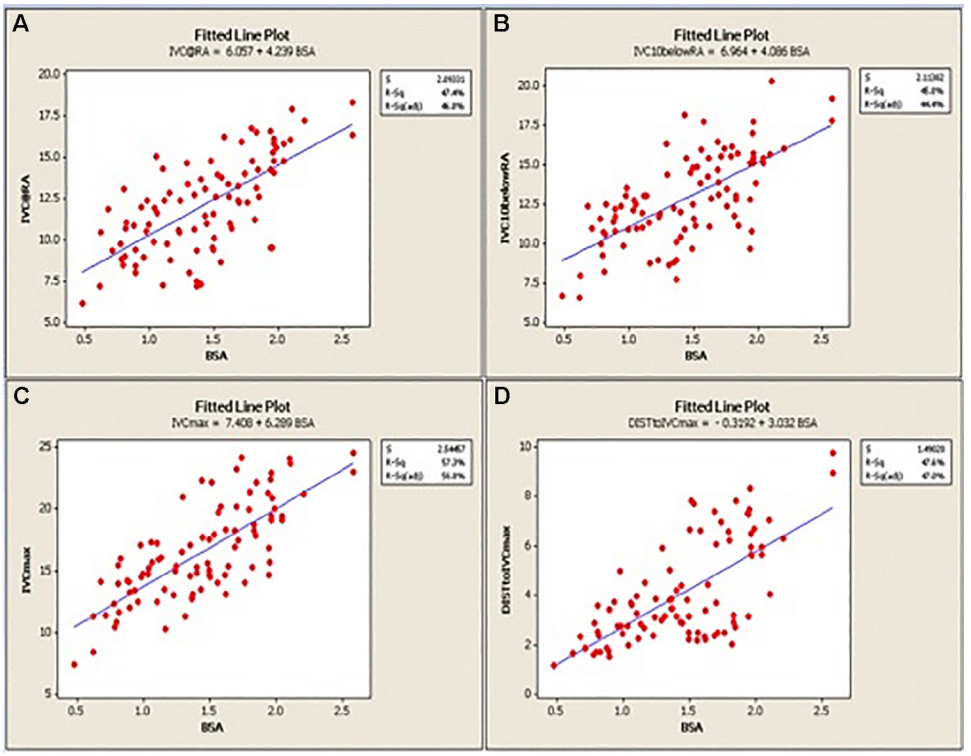

Figure 2. Regression models for **A,** IVC diameter at the IVC-RA, **B,** IVC diameter at IVC-RA10, **C,** IVCmax diameter, and **D,** IVCmax distance from the IVC-RA.

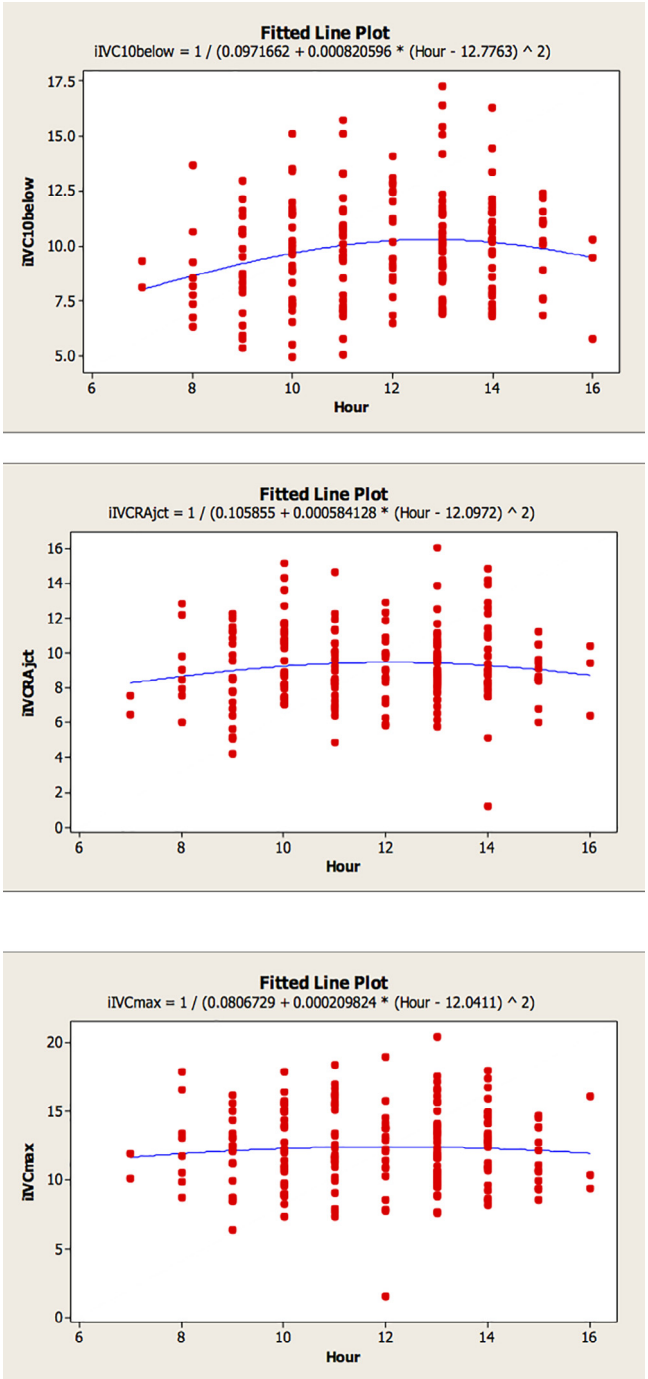

Figure 3. Associations between iIVC measurements and time of the day in normal controls and syncope subjects.

Table IV. Intraclass correlations and 95% CIs of intraobserver and interobserver concordance

	Intraobserver		Interobserver	
Measurements	**ICC**	**95% CI**	**ICC**	**95% CI**
IVC- RA	0.9565	0.8759-0.9852	0.8952	0.7172-0.9636
IVC-RA10	0.9799	0.9412-0.9932	0.9201	0.7793-0.9724
IVCmax	0.9888	0.9670-0.9962	0.9760	0.9301-0.9919
Distance from IVCmax to IVC-RA	0.9834	0.9513-0.9944	0.9546	0.8705-0.9845

ICC, intraclass correlation.

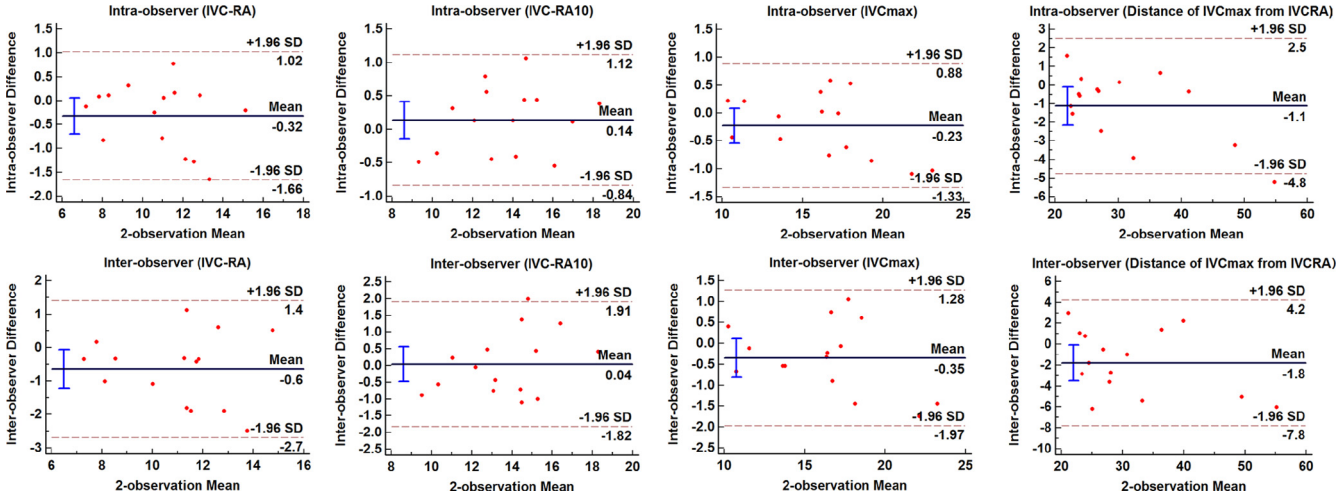

Figure 4. Bland-Altman plots of intraobserver measurement variability of IVC measurements.