Impaired endothelium-dependent vasodilatation is a novel predictor of mortality in intensive care*

Martin J. Duffy, MB; Brian A. Mullan, MD; Thelma R. Craig, MB; Murali Shyamsundar, MB; Rob E. MacSweeney, MB; Gillian Thompson; Michael Stevenson; Daniel F. McAuley, MD

Objective: **Endothelial function may be impaired in critical illness. We hypothesized that impaired endothelium-dependent vasodilatation is a predictor of mortality in critically ill patients.**

Design: **Prospective observational cohort study.**

Setting: **Seventeen-bed adult intensive care unit in a tertiary referral university teaching hospital.**

Patients: **Patients were recruited within 24 hrs of admission to the intensive care unit.**

Interventions: **The SphygmoCor Mx system was used to derive the aortic augmentation index from radial artery pulse pressure waveforms. Endothelium-dependent vasodilatation was calculated as the change in augmentation index in response to an endothelium-dependent vasodilator (salbutamol).**

Measurements and Main Results: **Demographics, severity of illness scores, and physiological parameters were collected. Statistically significant predictors of mortality identified using single regressor analysis were entered into a multiple logistic regression model. Receiver operator characteristic curves were generated. Ninety-four patients completed the study. There were 80 survivors and 14 nonsurvivors. The Simplified Acute Physiology Score II, the Sequential Organ Failure Assessment score, leukocyte count, and endothelium-dependent vasodilatation conferred an increased risk of mortality. In logistic regression analysis, endothelium-dependent vasodilatation was the only predictor of mortality with an adjusted odds ratio of 26.1 (95% confidence interval [CI], 4.3–159.5). An endothelium-dependent vasodilatation value of 0.5% or less predicted intensive care unit mortality with a sensitivity of 79% (CI, 59–88%) and specificity of 98% (CI, 94–99%).**

Conclusions: In vivo **bedside assessment of endothelium-dependent vasodilatation is an independent predictor of mortality in the critically ill. We have shown it to be superior to other validated severity of illness scores with high sensitivity and specificity. (Crit Care Med 2011; 39:629–635)**

KEY WORDS: ICU mortality; endothelial function; pulse wave analysis; endothelium-dependent vasodilatation

The endothelium plays a key role in the maintenance of vascular homeostasis (1). It regulates vascular tone, platelet aggregation, coagulation, fibrinolysis, and leukocyte activation. Endothelial dysfunction characterized by impaired endothelium-dependent vasodilatation (EDV) has been shown to occur early in a number of disease states, including acute systemic inflammation (2), and is predictive of outcome in patients with cardiovascular disease (3). The ability of EDV to predict outcome in critical illness has not previously been reported.

EDV may be assessed *in vivo* using techniques such as flow-mediated dilation, limb plethysmography, or cardiac catheterization. These techniques can be difficult to perform in the intensive care unit (ICU) and require an experienced operator. Pulse wave analysis (PWA) is a relatively new technique that uses a validated transfer function to calculate the central aortic waveform from a peripheral arterial pressure waveform (4). The transfer function is a mathematical model used to describe the relation between the central and peripheral arterial waveforms. Features of the central aortic waveform are illustrated in Figure 1 (5). Augmentation is defined as the difference between the second systolic peak (caused by wave reflection) and the first systolic peak (caused by left ventricular contraction). The augmentation index (AIx) is this difference expressed as a percentage of the central pulse pressure. The central aortic pressure waveform changes during vasodilatation such that the AIx falls (Fig. 2) (6). Salbutamol is an endothelium-dependent vasodilator that releases nitric oxide from the endothelium (7). EDV is calculated as the fall in AIx (%) after salbutamol administration and is also expressed as a percentage. PWA combined with provocative salbutamol testing has been shown to be a simple, repeatable technique for assessing systemic endothelial function *in vivo* in patients with cardiovascular disease or risk factors for cardiovascular disease (8–10). There is limited information on the use of this technique in patients with critical illness.

Prediction of outcome in the critically ill is difficult. Severity of illness scores, including the Acute Physiology and Chronic Health Evaluation II score, the Simplified Acute Physiology Score II (SAPS II) and the Sequential Organ Failure Assessment score, have been validated as reliable and accurate in cohorts of ICU patients but have limited use in predicting outcome for individual patients (11–14). The urinary albumin:

***See also p. 878.**

From the Regional Intensive Care Unit (MJD, BAM, TRC, MS, REM, GT, DFM), Royal Victoria Hospital, Belfast, UK; the Centre for Infection and Immunity (MJD, BAM, TRC, MS, REM, DFM), The Queen's University Belfast, UK; and the Epidemiology Research Group (MS), Mulhouse, Royal Victoria Hospital, Belfast, UK.

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M.J.D. and B.A.M. contributed equally to this work.

For information regarding this article, E-mail: brian.mullan@belfasttrust.hscni.net

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creatinine ratio has been shown to be a surrogate marker of systemic endothelial dysfunction (15). Microalbuminuria has been reported in different clinical scenarios involving endothelial damage including trauma, surgery, burns, and acute respiratory distress syndrome (15–18) but is limited in that this as well as other surrogate biochemical biomarkers cannot be measured in real time. PWA has potential advantages over other techniques in that it is easy to perform and it can be done *in vivo* at the bedside. We tested the hypothesis that measurement of EDV using PWA predicts mortality in critically ill adults.

MATERIALS AND METHODS

Design

This was a prospective study conducted from July 2007 to December 2008. For the purpose of this study, critical illness was defined as a need for intensive care for >24 hrs. Informed and written consent was obtained from the patient's legal representative on admission and from the patient after their discharge from the ICU when possible. Treating clinicians were blinded to study measurements. The study received ethical approval from the Northern Ireland Research Ethics Committee (07/NIR03/30) and was International Standard Randomized Controlled Trial-registered (ISRCTN49531007).

Subjects

Adult patients admitted to the Regional Intensive Care Unit in the Royal Victoria Hospital, Belfast, were considered for inclusion in the study. This is a 17-bed unit in a tertiary university teaching hospital. Patients were excluded if they were transferred from another ICU, if they were pregnant, if radial arterial access was unavailable, if they had an allergy/contraindication to salbutamol, if they had a do-not-resuscitate order in place, or if consent was unavailable/declined. Patients who were unlikely to survive or likely to be discharged within 24 hrs of ICU admission were excluded because their outcome would be known at the time of recruitment, effectively unblinding the researcher to the primary outcome measure. Other exclusions are listed in Figure 3.

Data Collection

Demographics. Baseline demographic data were collected for all recruited patients. Routine hematology and biochemical indices were measured. Medical conditions and treatments known to affect endothelial function before critical illness were noted.

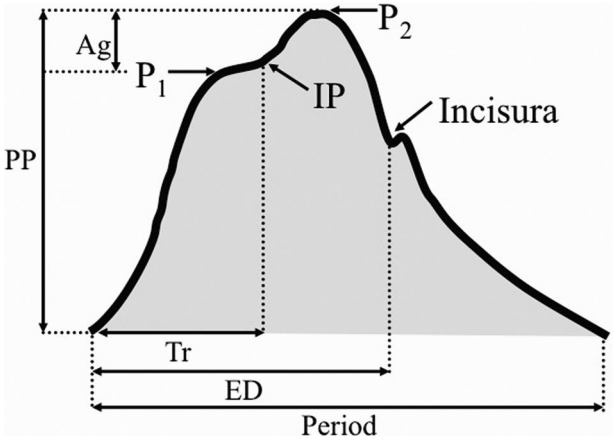

Figure 1. The central aortic pressure waveform. *P1*, first systolic peak; *P2*, second systolic peak; *IP*, inflection point; *Ag*, augmentation (P2–P1); *PP*, pulse pressure; *Tr*, time to wave reflection; *ED*, ejection duration. The aortic augmentation index (*AIx*) = Ag/PP.

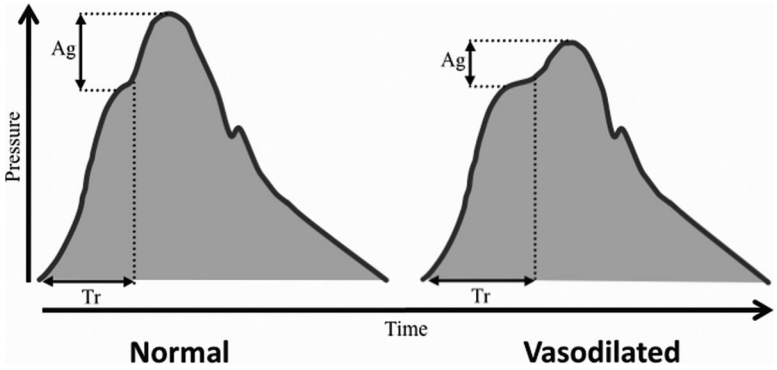

Figure 2. Change in central waveform after vasodilatation. The normal waveform shown on the left changes in response to vasodilatation such that there is a decrease in augmentation (*Ag*) and wave amplitude. The result of these is a fall in augmentation index (*AIx*) and this difference is the endothelium-dependent vasodilation (*EDV*). *Tr*, time to wave reflection.

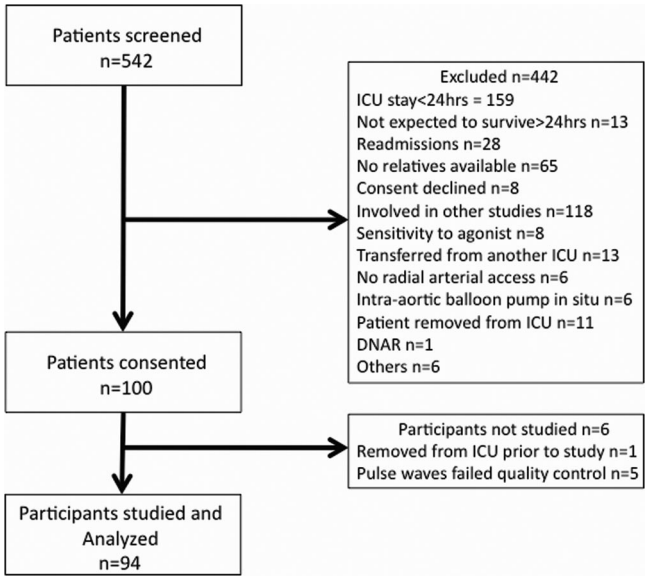

Figure 3. Study flow diagram of patient screening and recruitment. *ICU*, intensive care unit; *DNAR*, do not resuscitate.

Acute Physiology and Chronic Health Evaluation II/SAPS II/Sequential Organ Failure Assessment Scores. The Acute Physiology and Chronic Health Evaluation II and SAPS II scores were calculated from data during the patients' first 24 hrs of admission to the ICU. These scores were then used to calculate predicted mortality. Sequential Organ Failure Assessment scores were calculated at the time of bedside assessment.

Pulse Wave Analysis. This was performed with the SphygmoCor Mx System (AtCor Medical, Sydney, Australia). An indwelling 20-g radial arterial catheter was used to obtain a calibrated peripheral arterial pressure waveform. The central aortic waveform was derived from the peripheral arterial waveform using a validated transfer function (19–21). In addition, the SphygmoCor Mx System contains quality control software with pulse variation <5% considered acceptable. The aortic AIx is calculated and corrected to a heart rate to 75 beats/min^{-1}.

PWA was performed for 5 mins to establish a stable baseline under direct observation with the SphygmoCor Mx averaging waveforms over 1 min. Measurements were started after this period. After this, each patient received 2.5 mg nebulized salbutamol. The maximal change in AIx was recorded at 20 mins, as previously described (7).

Urine Analysis. Ten milliliters of urine was collected from the patient's self-retaining urinary catheter using a standard aseptic technique. Albumin was measured in urine using a commercially available immunoturbidimetric assay containing antibody specific for human albumin (Randox Laboratories Ltd, Crumlin, UK). Creatinine was measured using a modified Jaffe method as previously described (Roche Diagnostics, Indianapolis, IN) (22).

Plasma Salbutamol Analysis. Twenty mins after the administration of nebulized salbutamol, a blood sample was collected from the indwelling arterial catheter. This was centrifuged at 2000 rpm for 10 mins at 10°C and the plasma was then stored at −80°C. Plasma salbutamol concentrations were subsequently measured in batches using a commercially available quantitative enzyme-linked immunosorbent assay (Bio-X Diagnostics, Jemelle, Belgium).

Statistical Analysis

ICU mortality was the primary outcome in this study. Patients were classified as ICU survivors or nonsurvivors. Mean (SD) or median (interquartile range) was used as appropriate after testing for normality with Kolmogorov-Smirnov and Shapiro-Wilk tests. Categorical variables were compared using Fisher's exact test. Continuous normally distributed variables were compared using a Student's *t* test and the Mann-Whitney *U* test was used for nonparametric variables. Paired tests were used to compare changes after salbutamol administration. Where outlying values skewed data in either group, logarithms were used to minimize this effect rather than excluding such outliers.

To analyze ICU mortality, a forward stepwise logistic regression model was used to choose from variables that were statistically associated with mortality. Adjusted odds ratio and 95% confidence interval (CI) per unit change are presented. Receiver operator characteristic curves were also plotted for predictive indices. Statistical analysis was performed with SPSS Statistics version 18.0 for Mac OS X (SPSS Inc, Chicago, IL) and graphs generated using Prism 5 for Mac OS X, Version 5.0b (GraphPad Software Inc, La Jolla, CA). Results were deemed to be statistically significant for $p < .05$.

RESULTS

One hundred patients were prospectively identified and recruited into the study. Of these, 94 completed the study and had data recorded for analysis (Fig. 3). The demographics and historical variables of participants are shown in Table 1. The most prevalent condition in the patients' medical history was hypertension (28%). Other risk factors for cardiovascular disease included smoking (39%), hypercholesterolemia (15%), and diabetes (1%). The most frequently prescribed medications before ICU admission were β-blockers (16%) and statins (15%). A summary of admission diagnoses is shown in Table 2.

There were 14 nonsurvivors and 80 survivors to ICU discharge. The time from ICU admission to study measurement was 16.0 (12.0, 22.0) hrs for survivors and 16.4 (8.8, 19.3) hrs for nonsurvivors ($p = .79$). The baseline physiological variables are shown in Table 3.

Baseline AIx was similar between survivors and nonsurvivors ($p = .86$; Table 3). After salbutamol administration, AIx fell in the survivors ($p < .001$) but remained unchanged in the nonsurvivors ($p = .1$; Fig. 4). EDV was significantly higher in survivors (4.5% [2.0, 8.0]) compared with nonsurvivors (0% [0, 0.3]; $p < .001$). Plasma salbutamol levels were similar in both groups (2.2 [1.9] ng/mL vs. 2.9 [2.1] ng/mL, $p = .2$).

Using single regressor analysis, only four variables were associated with increased ICU mortality; these were the SAPS II score, the Sequential Organ Failure Assessment score, the leukocyte count, and EDV (Table 3). Although the Acute Physiology and Chronic Health Evaluation II score and the $\log_{10}$ urinary albumin:creatinine ratio were higher in nonsurvivors, this did not reach statistical significance (Table 3).

Logistic regression analysis included the variables shown to predict mortality from univariate analysis. This included both SAPS II score and leukocyte count. To disaggregate these variables, the contribution of leukocyte count to the SAPS II score was removed and the SAPS II without leukocyte count used in the analysis. This regression revealed EDV to be the only independent predictor of mortality in the ICU with an adjusted odds ratio (95% CI) of 26.1 (4.3–159.5; $p < .001$) per 1% reduction in EDV.

Receiver operator characteristic curves were generated to compare the predictive ability of each index to discriminate between survivors and nonsurvivors (Fig. 5). The area under the curve (95% CI) was highest for EDV (96.9% [93.6–100.0%]). From this curve, the optimal cutoff value for EDV as a predictor of mortality was 0.5%. An EDV of 0.5% or less predicted ICU mortality with a sensitivity of 79% (CI, 59–88%) and specificity of 97.5% (CI, 94.1–99.2%).

DISCUSSION

This observational study has demonstrated that impaired EDV is an independent predictor of mortality in critical illness. It provides an *in vivo* bedside assessment of systemic endothelial function. It has the potential to be used as an outcome measure for pharmacologic agents using the endothelium as a therapeutic target. As a clinical tool it may assist the intensivist in identifying those patients at greater risk of death early in the course of their ICU stay.

This is the first clinical study to describe the use of this technique to assess systemic endothelial function in ICU. Although it may have been preferable for all assessments to be made within a shorter time scale of <24 hrs, the use of a shorter time window would have resulted in more excluded cases given the obligation and time required to gain legal representative consent, which was not necessary in previous studies in which consent was waived (23). A 24-hr limit for recruitment allowed a more representative cohort of patients to be assessed and permitted comparison with outcome predictors such as the Acute Physiology and Chronic Health Evaluation II score, which is calculated from data collected over the first 24 hrs of ICU admission.

Table 1. Demographic factors of study participants

Baseline Variable	Entire Group (n = 94) Median (IQR) or No. (%)	Survivors (n = 80) Median (IQR) or No. (%)	Nonsurvivors (n = 14) Median (IQR) or No. (%)	p
Demographics				
Age, yrs	61 (49, 76)	61 (49, 76)	65 (46, 76)	.78
Height, m	1.73 (1.65, 1.76)	1.74 (1.65, 1.77)	1.67 (1.61, 1.77)	.27
BMI, (kg/m^2)	26 (24, 28)	26 (24, 28)	25 (23, 27)	.27
Gender, male/female	69:25	61:19	8:6	.14
Medical history				
Cardiovascular	18 (19.1%)	15 (18.8%)	3 (21.4%)	.82
Hepatic	6 (6.4%)	4 (5.0%)	2 (14.3%)	.2
Musculoskeletal	4 (4.3%)	4 (5.0%)	0 (0%)	.4
Pulmonary	13 (13.8%)	12 (15.0%)	1 (7.1%)	.44
Gastrointestinal	4 (4.3%)	3 (3.8%)	1 (7.1%)	.56
Renal	2 (2.1%)	2 (2.5%)	0 (0%)	.55
Dermatological	1 (1.0%)	1 (1.3%)	0 (0%)	.68
Endocrine	3 (3.2%)	3 (3.8%)	0 (0%)	.46
Risk factors associated with endothelial dysfunction				
Smoking	37 (39.4%)	31 (38.8%)	6 (42.9%)	.77
Hypertension	26 (27.7%)	24 (30.0%)	2 (14.3%)	.23
Hypercholesterolemia	14 (14.9%)	11 (13.8%)	3 (21.4%)	.46
Diabetes	1 (1.0%)	1 (1.3%)	0 (0%)	.68
Preadmission medication				
Salbutamol	8 (8.5%)	6 (7.5%)	2 (14.3%)	.4
Steroids	5 (5.3%)	4 (5.0%)	1 (7.1%)	.74
Statins	14 (14.9%)	11 (13.8%)	3 (21.4%)	.46
Anticoagulants	12 (12.8%)	10 (12.5%)	2 (14.3%)	.85
Dietary supplements	2 (2.1%)	1 (1.3%)	1 (7.1%)	.16
Anxiolytics	2 (2.1%)	1 (1.3%)	1 (7.1%)	.16
Diuretics	9 (9.6%)	8 (10%)	1 (7.1%)	.74
β-blockers	15 (16.0%)	12 (15%)	2 (21%)	.73
ACE inhibitors	3 (3.2%)	3 (3.8%)	0 (0%)	.46
Nitrates	2 (2.1%)	2 (2.5%)	0 (0%)	.55
Calcium channel antagonists	1 (1.0%)	1 (1.3%)	0 (0%)	.68

IQR, interquartile range; BMI, body mass index; ACE, angiotensin-converting enzyme.

Table 2. Summary of clinical classification of patients studied

Surgical	No.	Deaths	Medical[a]	No.	Deaths
Gastrointestinal	10	0	Pneumonia	20	5
Thoracic	3	0	Respiratory failure	5	0
Neurosurgical	31	6	AMI/cardiac failure	5	2
Polytrauma	7	0	Neurologic	5	0
Burns	1	1	Sepsis	3	0
			Meningitis	1	0
			Pancreatitis	1	0
			Hepatic failure	1	0
Total	52	7	Total	42	7

AMI, acute myocardial infarction.

[a]Respiratory failure includes patients with noninfectious etiology of respiratory failure resulting from chronic obstructive pulmonary disease, aspiration pneumonitis, and musculoskeletal compromise; pneumonia refers to primary pneumonia; polytrauma includes nonisolated head injuries and long bone and facial fractures.

Salbutamol is a β_2 agonist, which acts as an endothelial-dependent vasodilator. In sepsis, an attenuated response to β stimulation has been reported at the β-receptor as well as postreceptor level (24). In this cohort of intensive care patients, however, there was no difference in the prevalence of sepsis between survivors and nonsurvivors suggesting that the difference in vascular responsiveness was unrelated to variation in β-receptor sensitivity. In sepsis and sepsis inflammatory response syndrome, the vasculature may already be maximally vasodilated and therefore the response to a vasodilator might be attenuated in this setting. In contrast, the pharmacologic effect of pressor agents would cause an increase in arterial tone, which would cause an increase in baseline recordings of pressure and augmentation. However, because systemic arterial tone (as assessed from baseline AIx) was not different between the groups ($p = .86$; Table 3), and similarly to sepsis, the use and dosage of vasopressors was not different between survivors and nonsurvivors (Table 3), this is unlikely to account for the difference seen in endothelial-dependent vasodilation.

The administration of salbutamol in critical care is common. For salbutamol to have an effect at the endothelium, there has to be transfer across the pulmonary circulation and distribution to the systemic circulation. This requires adequate ventilation and perfusion, both of which can become impaired in critical illness. Pulmonary function as assessed by the P_{IO_2}:F_{IO_2} ratio was similar between survivors and nonsurvivors at the time of bedside assessment ($p = .49$; Table 3). Previous studies have demonstrated that critically ill patients with respiratory failure have physiologically efficacious plasma levels of the β-agonist after nebulized administration (25). Of note, plasma salbutamol levels were not significantly different between survivors and nonsurvivors in the present study.

The transfer function applied to the peripheral radial pulse waveform was not derived from studies in critically ill individuals. Even if the derived aortic variables obtained using the transfer factor were not exactly the same as those obtained by direct invasive measurement, the technique should effectively monitor the change in hemodynamics from baseline with intervention. Validation studies in which vasodilators and/or vasoconstrictors were administered to subjects have all shown direct correlation between changes in central aortic hemodynamics and those derived from PWA (19, 26).

Correction of augmentation index to a heart rate of 75 beats/min^{-1} is important because this variable changes in response to heart rate. Previous studies have described an inverse linear relationship between heart rate and augmentation index whereby for each 10 beats/min^{-1} rise in heart rate the augmentation index falls by 4% (27). An increase in heart rate shortens the duration of systole so that reflected waves are more likely to arrive at the ascending aorta in diastole and during the fall of the incident wave of systole. Hence, there

Table 3. Baseline variables at the time of endothelial function assessment

	Entire Group (n = 94) Mean (SD) Median (IQR) or No. (%)	Survivors (n = 80) Mean (SD) Median (IQR) or No. (%)	Nonsurvivors (n = 14) Mean (SD) Median (IQR) or No. (%)	*p*
Severity of illness scores.				
APACHE II	16 (12, 22)	14 (12, 22)	18 (13, 26)	.14
SAPS II	43 (35, 53)	42 (34, 51)	49 (43, 59)	.03
SOFA	7 (6, 9)	7 (6, 8)	9 (7, 10)	.03
Physiological indices				
Heart rate, beats/min	82 (63, 97)	82 (63, 98)	76 (62, 90)	.37
MAP, mm Hg	86 (77, 97)	86 (77, 96)	90 (77, 97)	.87
AIx, %	21 (4, 33)	21 (5, 33)	20 (3, 39)	.86
EDV, %	3 (1.0, 7.3)	4.5 (2.0, 8.0)	0.0 (0.0, 0.3)	<.001
Pao_2:FIo_2 ratio, mm Hg	216.4 (89.9)	213.7 (89.4)	231.9 (94.5)	.49
Hematologic				
Hemoglobin, g/dL	10.4 (2.5)	10.4 (2.6)	10.6 (1.8)	.75
Platelet count, $\times 10^9$/mL	204 (147, 279)	205 (148, 268)	203 (131, 477)	.75
Leukocyte count, $\times 10^9$/mL	11.3 (8.6, 15.7)	10.5 (8.1, 15.2)	14.3 (11.0, 21.6)	.01
Biochemistry				
Creatinine, mmol/L	75 (57, 104)	73 (59, 97)	91 (42, 116)	.52
Glucose, mmol/L	7.2 (6.1, 9.0)	7.2 (6.1, 9.0)	7.1 (6.1, 8.6)	.93
HbA_{1C}, %	5.4 (5.2, 5.8)	5.4 (5.2, 5.8)	5.4 (5.2, 5.7)	.96
ACR, mg/mmol	3.1 (1.2, 6.3)	2.29 (1.0, 6.6)	5.1 (2.7, 6.4)	.06
Interventions				
Mechanical ventilation	92 (97.9%)	79 (98.8%)	13 (92.9%)	.28
Vasoactive therapy				
Patients receiving norepinephrine	29 (30.9%)	23 (28.8%)	6 (42.9%)	.35
Dose in patients receiving norepinephrine, μg/kg/min	0.10 (0.05, 0.12)	0.08 (0.05, 0.11)	0.11 (0.09, 0.20)	.10
Patients receiving dobutamine	5 (5.3%)	3 (3.8%)	2 (14.3%)	.20
Dose in patients receiving dobutamine, μg/kg/min	2.9 (1.9, 6.2)	2.9 (1.6, 9.5)	2.6 (2.3, 3.0)	.57

IQR, interquartile range; APACHE II, Acute Physiology and Chronic Health Evaluation II; SAPS II, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment; MAP, mean arterial pressure; AIx, augmentation index; EDV, endothelial-dependent vasodilatation; HBA_{1C}, glycosylated hemoglobin; ACR, albumin:creatinine ratio.

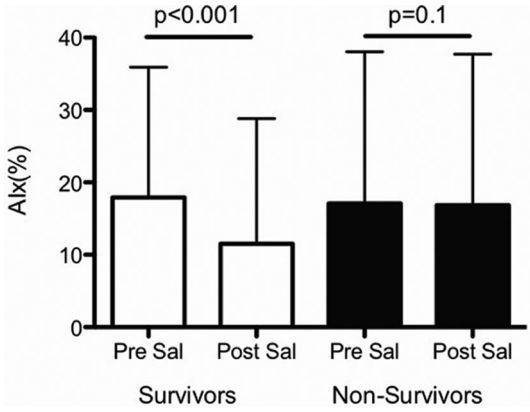

Figure 4. In intensive care unit survivors, there is a significant fall in augmentation index (*AIx*) in response to salbutamol from 17.9% (18.0%) to 11.5% (17.3%), $p < .001$, indicating vasodilatation. This response is lacking in nonsurvivors in whom AIx at baseline is 17.1% (21.0%) and after salbutamol stimulation is 16.9% (20.9%), $p = .1$, indicating endothelial dysfunction.

is a fall in wave augmentation caused by tachycardia. The reverse is true for bradycardia. This linear relationship holds for heart rates up to 120 beats/min^{-1}. Beyond this, the relationship may be nonlinear (28). Normalization calculations are performed automatically by the SphygmoCor Mx system software, which calculates the derived waveform for a heart rate 75 beats/min^{-1}. No correction is needed for the first systolic peak and aortic diastolic blood pressure because these parameters are not affected by heart rate (29). Pauca et al (6) demonstrated equivalence between measured and derived aortic waveforms in patients with irregular heart rates.

Pharmacologic agents used to induce EDV *in vivo* include acetylcholine (30), methacholine (31), and bradykinin (32). Nonpharmacologic interventions include flow-mediated dilation induced by reactive hyperemia-associated transient regional blood flow occlusion (33). These techniques demonstrate EDV in regional conduit arterial vessels, typically the brachial artery. EDV is assessed in such cases by measurement of changes in arterial diameter with ultrasound or blood flow by plethysmography. Many such vasodilators cannot be given systemically to the critically ill patient in intensive care as a result of their adverse effect profiles. Similar to our findings, salbutamol can be given safely to the intensive care patient (34). EDV induced by salbutamol is comparable to that measured by other means as described by Lind et al (35).

As part of this study, we wanted to compare the performance of other reported predictors of outcome. Severity of illness score, although not intended to predict outcomes in individual patients, has been incorporated into clinical decision models (29). In this study, and in keeping with previous studies, these scores were higher in nonsurvivors. However, their predictive value was not maintained after logistic regression analysis. Similarly, leucocytosis has been reported as a predictor of mortality in pneumococcal sepsis (30) and surgical infection (31). A recent retrospective ICU study demonstrated that both leucopenia and marked leucocytosis were predictors of mortality (32). A higher leukocyte count was demonstrated among nonsurvivors in this cohort, but its predictive value was not maintained after logistic regression analysis. Previous work by Gosling et al (23) has shown that the urinary albumin:creatinine ratio, as a measure of systemic endothelial dysfunction, measured within 15 mins of ICU admission, was predictive of outcome in surgical, trauma, and burns patients. Although there was a trend toward a higher albumin:creatinine ratio in nonsurvivors in the present study, the result was not statistically significant. This difference between studies may be the result of the different patient cohorts. It should be noted that in the Gosling study, albumin:creatinine ratio was not predictive of outcome in patients with medical conditions. Overall on the

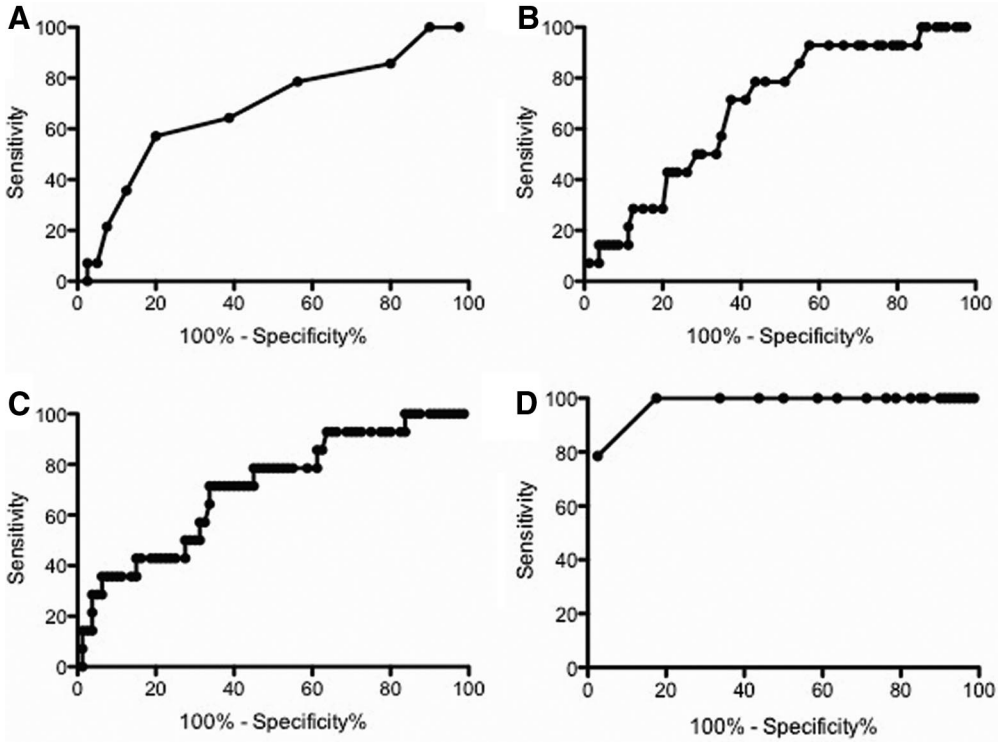

Figure 5. Receiver operator characteristic curves with respective areas under curve (95% confidence interval) for (*A*) Sequential Organ Failure Assessment score 68.1% (52.1, 84.2), $p = .03$; (*B*) Simplified Acute Physiology Score II score 68.5% (55.0, 82.1); $p = .03$ (*C*) leukocyte count 70.7% (56.2, 85.3), $p = .01$; and (*D*) endothelium-dependent vasodilation 96.9% (93.6, 100.0), $p < .001$.

basis of our findings, EDV appears to be superior in the prediction of outcome in the critically ill.

The present study is limited in that only 17% of screened patients were recruited. We have, however, demonstrated a heterogenous group of critically ill patients with diverse diagnoses representative of the case mix encountered in this unit. The mortality rate in study participants was 15% giving a limited number of events for analysis. This was comparable to the overall mortality rate (16%) for the period of the study.

An important consideration relates to whether this technique might be used as a noninvasive measure without the need for arterial cannulation. Surface tonometry has been used to measure the peripheral pulse waves in other studies (5). A previous study by Davis et al (36) used peripheral arterial tonometry to demonstrate endothelial dysfunction in sepsis within intensive care. The technique in that study used reactive hyperemia and a digital plethysmograph to measure regional EDV in the upper limb. A limitation of this method is that it only provides an assessment of regional EDV. However, tonometry use in intensive care may be problematic because calibration relies on the accuracy of blood pressure measurements with either noninvasive brachial sphygmomanometry or digital plethysmograph, which may be unreliable compared with intra-arterial measurements (37). Furthermore, surface tonometry also introduces interuser variability (38). Therefore, although surface tonometry combined with noninvasive blood pressure measurements may provide a potential method for endothelial assessment, in the critically ill in which invasive blood pressure measurement is the standard of care, it is unlikely to offer advantages to, or perform as well as, the technique described.

In the current study, endothelial function was assessed at one time point. Given the predictive ability of this technique, future studies should include repeated assessments to provide important information on what dynamic changes occur during critical illness. In this study, there were no correlations found EDV or any other marker of organ injury. Future longitudinal studies may indicate what conditions and treatments impact on endothelial function in the ICU.

CONCLUSIONS

EDV, as assessed by PWA, is an independent predictor of mortality in intensive care. We have shown it to be superior to other validated severity of illness scores and it is highly sensitive and specific. *In vivo* bedside assessment of systemic endothelial function may enable improved stratification of the critically ill and the targeting of new endothelial therapies in critical illness.

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