

Relationship between albumin excretion rate and aortic stiffness in untreated essential hypertensive patients

G. MULÈ, S. COTTONE, A. VADALÀ, V. VOLPE, G. MEZZATESTA, R. MONGIOVÌ,
G. PIAZZA, E. NARDI, G. ANDRONICO & G. CERASOLA

From the Dipartimento di Medicina Interna, Malattie Cardiovascolari e Nefrourologiche, Cattedra di Medicina Interna e Centro Ipertensione, Università di Palermo, Palermo, Italy

Abstract. Mulè G, Cottone S, Vadalà A, Volpe V, Mezzatesta G, Mongiovì R, Piazza G, Nardi E, Andronico G, Cerasola G (Cattedra di Medicina Interna e Centro Ipertensione, Università di Palermo, Italy). Relationship between albumin excretion rate and aortic stiffness in untreated essential hypertensive patients. *J Intern Med* 2004; **256**: 22–29.

Objectives. To evaluate, in a group of nondiabetic essential hypertensive patients with normal renal function, the relationship between albumin excretion rate (AER) and carotid-femoral pulse wave velocity (PWV), as an index of aortic stiffness.

Design. Cross-sectional study.

Setting. Outpatient hypertension clinic.

Subjects. Seventy patients with mild-to-moderate essential hypertension, aged 42 ± 8 years, never pharmacologically treated. All subjects underwent routine laboratory tests, 24-h ambulatory blood pressure (BP) monitoring, measurement of carotid-femoral PWV, by means of a computerized method, and AER.

Results. Microalbuminuric patients ($\text{AER} \geq 20 \mu\text{g min}^{-1}$; $n = 19$), when compared with

normoalbuminuric subjects, showed more elevated 24-h BP ($136/88 \pm 10/10$ vs. $128/83 \pm 7/6$ mmHg; $P < 0.001$ and $P = 0.013$, for systolic and diastolic BP respectively) and higher values of carotid-femoral PWV ($10.4 \pm 2 \text{ m s}^{-1}$ vs. 9.2 ± 1.3 ; $P = 0.006$). This latter difference remained statistically significant, even after correction by ANCOVA for 24-h systolic and diastolic BP, and body mass index (BMI, $P = 0.016$). Univariate regression analysis disclosed a tight correlation between AER and carotid-femoral PWV ($r = 0.42$; $P = 0.0003$). This association was confirmed in a multiple regression model ($\beta = 0.35$; $P = 0.009$) in which, as independent variables, besides PWV, 24-h BP, age, serum glucose values, smoking status, gender and BMI, were added.

Conclusions. Our results seem to confirm that microalbuminuria may represent the early renal manifestation of a widespread vascular dysfunction, and therefore it is an integrated marker of cardiovascular risk.

Keywords: aortic stiffness, arterial hypertension, cardiovascular risk, microalbuminuria, pulse wave velocity.

Introduction

It has been clearly demonstrated that microalbuminuria is an early sign of increased risk for developing overt nephropathy and cardiovascular disease in type 1 and type 2 diabetes [1]. Recently, a large body of evidence has been published suggesting that the value of microalbuminuria as predictor of organ damage [2–10] and of cardiovascular events and total mortality [11–18] may be extended

to nondiabetic subjects and to patients with essential hypertension. In some of these studies [17–18] the relationship of albumin excretion rate (AER) with cardiovascular complications was already apparent at levels of albuminuria currently considered to be normal (i.e. in timed urine collections $< 20 \mu\text{g min}^{-1}$).

Large artery stiffening plays an important role in cardiovascular diseases, and there is an increasing interest on noninvasive methods of measurement of

arterial compliance. Most of them are complex or need sophisticated technical equipment, which limits their application in clinical practice. Amongst the simplest method of evaluating arteries, pulse wave velocity (PWV) measurement is widely used as an index of large artery compliance [19]. The basic principle of PWV assessment is that the pulse wave runs along with the arterial tree at a speed, which depends upon the elasticity of the wall itself: the stiffer (i.e. less elastic) the wall the higher the velocity of propagation. PWV measured along the aortic and aortoiliac pathway is the most clinically relevant as the aorta and its first branches are responsible for most of the pathophysiological effects of arterial stiffness [19]. This surrogate index of aortic compliance has been shown to predict cardiovascular mortality in end-stage renal disease [20], in patients with essential hypertension [21] and in subjects with diabetes and glucose intolerance [22].

It has long been recognized that PWV is increased in kidney diseases, and the association of impaired renal function with decreased arterial elasticity is firmly established [19, 23].

In contrast, little is known about the relationships between microalbuminuria and large-artery stiffness [24–29].

Accordingly, the present study was undertaken to explore the relationships between AER and aortic PWV in a group of young and middle aged nondiabetic essential hypertensives with normal renal function.

Methods

The study population consisted of 70 essential hypertensives, aged between 23 and 61 years, referred to our outpatient hypertension centre, between October 2002 and July 2003. Patients with hypertension were included in the study, if they were newly diagnosed (within the previous 2 years), had never been previously pharmacologically treated, and had mild-to-moderate essential hypertension, as defined according to the 2003 European Society of Hypertension-European Society of Cardiology guidelines [30]. Exclusion criteria were: secondary or malignant hypertension, heart failure, positive history or clinical signs of ischaemic heart disease, cerebrovascular disease, renal insufficiency (serum creatinine: $>1.5 \text{ mg dL}^{-1}$ in men and

$>1.4 \text{ mg dL}^{-1}$ in women), overt proteinuria (AER $> 200 \text{ } \mu\text{g min}^{-1}$), major noncardiovascular diseases, dyslipidaemia requiring pharmacological treatment, and known diabetes or fasting glycaemia $\geq 126 \text{ mg dL}^{-1}$. Only patients with reliable urine collections were recruited.

Secondary hypertension was ruled out by clinical examination, and determination of serum creatinine, serum and urinary electrolytes, plasma renin activity, plasma aldosterone, plasma catecholamines and renal echography.

The local ethics committee approved the study protocol. Written informed consent was obtained from each patient.

In all subjects careful clinical history and physical examination were performed. Body weight and height were measured and body mass index (BMI) was calculated as weight to height squared.

Clinic blood pressure (BP) and heart rate were recorded by an automatic validated oscillometric device (Omron HEM 705 CP, OMRON Healthcare, Hamburg, Germany) [31], after the subject had been supine for 5 min. Three consecutive measurements were taken at 2-min intervals and averaged.

Moreover, fasting blood samples were taken to perform routine blood chemistry, and a 24-h urine sample was collected to evaluate the levels of microalbuminuria and creatinine. Twenty-four hour urine collection was repeated within 1 week to assay again microalbuminuria. Both urine collections were carried out on two nonworking days. The patients were advised to avoid excessive physical efforts on the day before and during the 24-h urine collections.

Microalbuminuria was analysed by a solid-phase enzyme immunoassay (Microalbumin-ELISA, DRG Diagnostics, Marburg, Germany). The sensitivity of this method is $0.5 \text{ } \mu\text{g mL}^{-1}$, and the intra-assay and interassay coefficient of variation were $\leq 3.6\%$ and $\leq 2.9\%$, respectively.

The average of two AER determinations was considered as the level of albuminuria in each subject.

The currently considered threshold for the definition of microalbuminuria [1] was used to separate microalbuminuric (AER $\geq 20 \text{ } \mu\text{g min}^{-1}$) from normoalbuminuric subjects (AER $< 20 \text{ } \mu\text{g min}^{-1}$).

In three subjects with urinary tract infections microalbuminuria was determined only after appropriate antibacterial treatment.

Determination of routine biochemical parameters was performed with standard techniques by using an autoanalyzer (Boehringer Mannheim for Hitachi system 911, Germany). Low-density lipoprotein (LDL) cholesterol was calculated by the Friedwald formula.

Aortic compliance was assessed by automatic carotid-femoral PWV measurement using the Complior® (Colson, Garges les Gonesse, France), a computerized device that allows on-line pulse wave recording and automatic calculation of PWV, as previously described and validated by Asmar *et al.* [32]. Aortic PWV was computed from the time delay between the recorded proximal (carotid) and distal (femoral) feet of the wave, and the superficially measured distance separating the respective pressure-sensitive transducers. It was determined as the average of at least 10 cardiac cycles. All measurements were carried out by the same observer (G.M.), unaware of the patient's AER data.

We performed a reproducibility study amongst eight participants, who underwent a second PWV evaluation within 1 week after the first examination. The mean (SD) difference between the two measurements was 0.32 (0.88) m s^{-1} . The mean intraobserver variability [(first measurement – second measurement/first measurement) \times %] was 3.37%.

Furthermore, all patients underwent 24-h ambulatory blood pressure monitoring (ABPM), by means of a portable noninvasive SpaceLabs 90207 recorder (Redmond, WA, USA). The device was applied in the morning to the nondominant arm and removed the next day at our hypertension unit.

Only records with more than 80% of valid data were accepted.

Statistics

The planned study sample size (70 participants) was calculated on the basis of previous investigations exploring the same issue [26, 27], assuming to find a coefficient of correlation between AER and PWV of at least 0.40. On this basis, it was estimated that the study would have 93% power to detect the expected result (with $\alpha = 0.05$).

Continuous variables were given as mean \pm SD, except for AER, which because of its skewed distribution, was expressed as the median and interquartile range. It was therefore log-transformed before starting the statistical tests.

Differences between groups were evaluated using the Student's *t*-test for unpaired data. Adjustment for some confounding variables was made by ANCOVA. For the categorical variables, comparisons were carried out using the chi-square test, with Yates' correction.

Simple and stepwise multiple regression analyses were used to test the relationships between microalbuminuria (log-transformed), PWV and other variables.

The null hypothesis was rejected at a two-tailed $P \leq 0.05$.

The statistical analyses were performed using the SYSTAT DATA software package, version 5.2 (Systat, Evanston, IL, USA).

Results

In the whole study population the median value (and interquartile range) of AER was 15.3 (6.6–27.2) $\mu\text{g min}^{-1}$ and the PWV was $9.6 \pm 1.7 \text{ m s}^{-1}$. Table 1 gives some clinical and demographic characteristics of the 70 patients included in the statistical analysis and of the microalbuminuric (AER $\geq 20 \mu\text{g min}^{-1}$) and normoalbuminuric subjects (AER $< 20 \mu\text{g min}^{-1}$). In the group of patients with higher AER a tendency towards greater values of BMI was observed. Moreover, clinic and 24-h systolic BP, as well as clinic mean BP and 24-h mean and diastolic BP, were significantly higher in the subset of microalbuminuric hypertensives. These latter showed also faster PWV ($10.4 \pm 2 \text{ m s}^{-1}$ vs. 9.2 ± 1.3 ; $P = 0.006$) (Fig. 1) when compared with normoalbuminuric subjects, even after adjustment by ANCOVA for 24-h systolic and diastolic BP, and BMI ($P = 0.016$).

Similar results were obtained when, instead of the traditional cut-off of $20 \mu\text{g min}^{-1}$, we used a lower limit that is the median value of AER ($15.3 \mu\text{g min}^{-1}$), to separate the study population into two subgroups. Indeed, PWV was higher in the subset of hypertensives with AER above the median ($n = 35$) when compared with those with AER below the median (10.2 ± 1.7 vs. $8.9 \pm 1.3 \text{ m s}^{-1}$; $P = 0.002$).

In our study population females were older than males (45.6 ± 8.5 vs. 40.3 ± 8.1 years; $P = 0.01$). No difference was found between males and females regarding PWV (9.7 ± 1.6 vs. $9.5 \pm 1.7 \text{ m s}^{-1}$). However, adjustment for age disclosed a trend

Table 1 Some demographic and clinical characteristics of the seventy subjects included in the analysis and of the microalbuminuric (AER ≥ 20 µg min⁻¹) and normoalbuminuric subjects (AER < 20 µg min⁻¹)

	Whole population (n = 70)	Normoalbuminuric subjects (AER < 20 µg min ⁻¹) (n = 51)	Microalbuminuric subjects (AER ≥ 20 µg min ⁻¹) (n = 19)	P-value
Age (years)	42.2 ± 8.1	42.4 ± 8.3	41.5 ± 7.7	0.682
Sex distribution (M/F) [n (%)]	44/26 (63/37)	31/20 (61/39)	13/6 (68/32)	0.757
Smokers [n (%)]				0.14*
Current	19 (27)	14 (27)	5 (26)	
Former	15 (21)	8 (16)	7 (37)	
Never	36 (52)	29 (57)	7 (37)	
Body mass index (kg m ⁻²)	26.9 ± 5.6	26.1 ± 5.7	28.8 ± 4.9	0.072
Glycaemia (mg dL ⁻¹)	90.6 ± 10.2	89.5 ± 9.8	92.8 ± 11	0.23
Total cholesterol (mg dL ⁻¹)	204.8 ± 38.2	208.1 ± 40.4	197.2 ± 32.2	0.295
Triglycerides (mg dL ⁻¹)	102.1 ± 44.1	102 ± 41.3	102.4 ± 51.3	0.973
HDL cholesterol (mg dL ⁻¹)	49.4 ± 11.4	50.1 ± 12.7	48 ± 7.7	0.502
LDL cholesterol (mg dL ⁻¹)	135 ± 32.4	137.7 ± 35.4	128.7 ± 23.7	0.31
Serum creatinine (mg dL ⁻¹)	0.81 ± 0.15	0.81 ± 0.16	0.82 ± 0.13	0.808
Creatinine clearance (mL min ⁻¹)	111.4 ± 28.3	108.1 ± 30.6	119 ± 20.7	0.157
Clinic systolic BP (mmHg)	147.4 ± 16	143.1 ± 16.5	151.9 ± 14.4	0.044
Clinic diastolic BP (mmHg)	95.4 ± 9.3	93.4 ± 9.6	97.7 ± 8.8	0.093
Clinic pulse pressure (mmHg)	52 ± 11.5	49.7 ± 13.9	54.2 ± 9.1	0.195
Clinic mean BP (mmHg)	112.7 ± 10.3	110 ± 10.3	115.7 ± 10.3	0.043
24-h systolic BP (mmHg)	131.5 ± 8.7	128.2 ± 7.4	135.8 ± 9.5	<0.001
24-h diastolic BP (mmHg)	85.2 ± 7.5	82.7 ± 6.1	87.6 ± 9.5	0.013
24-h pulse pressure (mmHg)	46.3 ± 6.2	45.5 ± 6.2	48.2 ± 5.9	0.105
24-h mean BP (mmHg)	100.6 ± 7.4	97.9 ± 5.9	103.5 ± 9.1	0.004
24-h heart rate (beats min ⁻¹)	75.2 ± 8.1	74.7 ± 8.3	76.2 ± 7.7	0.496

*Value obtained by chi-square test performed between the three subgroups of never, former and current smokers.

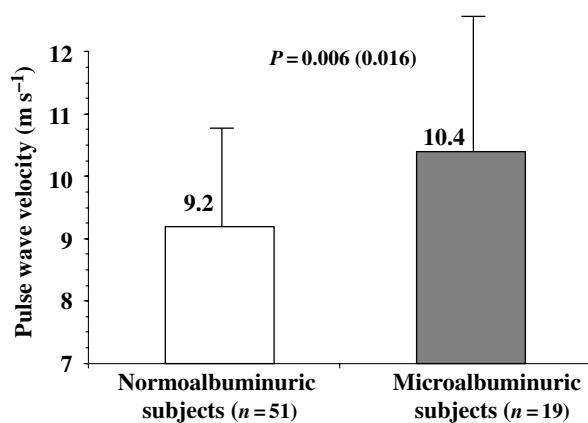


Fig. 1 Carotid-femoral pulse wave velocity (PWV) in normoalbuminuric and microalbuminuric essential hypertensives. The P-value in parentheses represents probability after adjustment, by ANCOVA, for 24-h systolic and diastolic blood pressures and body mass index.

towards faster PWV in males compared with females (9.9 ± 1.7 vs. 9.1 ± 1.6 m s⁻¹; P = 0.052). Moreover, AER was slightly higher in males than it was in females [15.4 (7.8–32.9) vs. 9.2 (3.3–15.3);

P = 0.03]. In current smokers PWV tended to be higher than it was in those who had never smoked (10.1 ± 1.8 vs. 9.2 ± 1.7; P = 0.06). On the contrary, no difference was found between these two subgroups with respect to AER [13.6 (7.4–18.4) vs. 14.1 (6.4–19.2)].

Simple regression analysis disclosed significant correlations between AER, PWV and some clinical and demographic variables, which are summarized in Table 2. Furthermore, a tight correlation between AER (log-transformed) and aortic PWV was found (r = 0.42; P = 0.0003) (Fig. 2). This association was confirmed (β = 0.35; P = 0.009) in a multiple regression model (R² = 0.44) in which, as independent variables besides PWV, all the parameters related to AER or PWV in univariate analyses (24-h systolic and diastolic BP, age, serum glucose values, smoking status, gender and BMI) were added. The inclusion into this model of clinic BP values, instead of 24-h ambulatory BP, did not significantly modify the results (β = 0.37; P = 0.007). The same was true when 24-h systolic and diastolic BP were replaced by 24-h pulse and

	PWV	P-value	(LOG) AER	P-value
Age	0.48	0.00003	-0.05	NS
Body mass index	0.32	0.007	0.27	0.02
Glycaemia	<i>0.23</i>	<i>0.055</i>	0.15	NS
Creatinine clearance	0.14	NS	0.30	0.01
Clinic systolic blood pressure	0.52	0.000004	0.31	0.009
Clinic diastolic blood pressure	0.34	0.004	0.37	0.002
Clinic pulse pressure	0.42	0.0003	0.13	NS
Clinic mean blood pressure	0.47	0.00004	0.37	0.002
24-h systolic blood pressure	0.49	0.00002	0.42	0.0003
24-h diastolic blood pressure	0.31	0.009	0.32	0.007
24-h pulse pressure	0.39	0.0008	0.25	0.037
24-h mean blood pressure	0.40	0.0006	0.37	0.002

Table 2 Univariate correlations between albumin excretion rate (AER), aortic pulse wave velocity (PWV) and some demographic and clinical variables in the whole study population ($n = 70$). Bold numbers represent correlations of statistical significance. Italic numbers indicate correlations of borderline statistical significance.

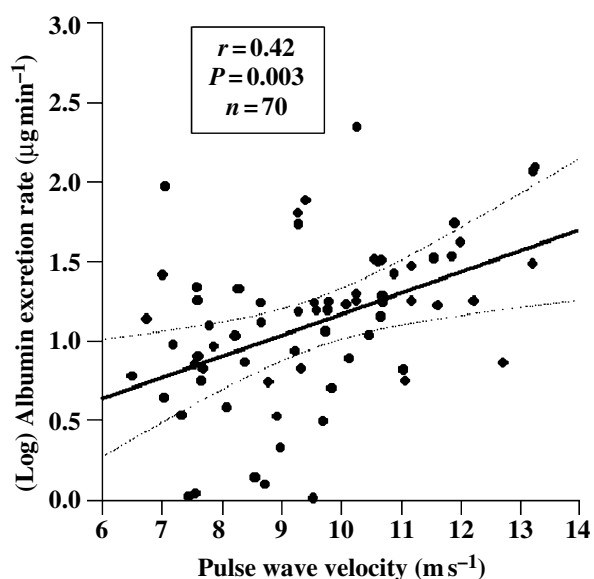


Fig. 2 Scatter-plot showing the relation between carotid-femoral pulse wave velocity and albumin excretion rate (transformed as a logarithm for its skewed distribution). Dashed hyperbolic lines represent the 95% confidence bands around the regression line.

mean pressures in the multiple regression model ($\beta = 0.37$; $P = 0.007$).

Discussion

Microalbuminuria may be considered a marker of vascular dysfunction, which is not confined to the renal arterial bed alone, whereas carotid-femoral PWV is an indicator of the aortic stiffness. Both these parameters have been identified as independent predictors of cardiovascular morbidity and mortality [1–22]. Nevertheless, the relationship between AER and large artery stiffening has not been fully elucidated.

Recently, in the Losartan Intervention for Endpoint reduction (LIFE) study, by using the pulse pressure/stroke index ratio (PP/SVi), as an approximate indirect estimate of the overall stiffness of the systemic arterial tree, Palmieri *et al.* found a tendency towards greater values of albuminuria in patients of the third tertile of PP/SVi, when compared with the lower tertiles, even if this difference was not statistically significant [24].

When more direct measures of aortic stiffness were employed a close association between AER and reduced aortic compliance was observed. For example, several years ago Takegoshi found a significant association between PWV and AER in 40 diabetic patients [25]. This finding was recently confirmed in 37 subjects with type 2 diabetes [26]. An even stronger correlation between these two variables was observed in a group of nonsmoking patients with essential hypertension [27]. Consistent with these reports Tsioufis *et al.* showed abnormal aortic root distensibility, assessed by transthoracic echocardiography, in microalbuminuric hypertensives when compared with normoalbuminuric ones [28]. The same authors documented more recently that an earlier systolic augmentation in the carotid arterial pressure contour (i.e. an increased augmentation index reflecting a more impaired arterial elasticity) was significantly and independently associated with greater values of AER in untreated patients with essential hypertension [29].

Our results seem to be in keeping with these previous data. Indeed, the main finding of the present study was the identification of a strong correlation between carotid-femoral PWV and AER in a sample of newly diagnosed and untreated nondiabetic hypertensive subjects. Moreover, the

results of multiple regression analysis showed that this association was independent of some potential confounders, known determinants of aortic compliance and/or microalbuminuria, such as BP, age, gender, smoking habits, BMI and glycaemia.

Moreover, splitting the study population in microalbuminuric and normoalbuminuric subjects we found greater values of aortic PWV in patients with microalbuminuria. Similar conclusions were obtained when the subjects were divided into two subgroups on the basis of the median value of the distribution of AER ($15.3 \mu\text{g min}^{-1}$), that is below the currently considered threshold for the definition of microalbuminuria ($20 \mu\text{g min}^{-1}$). Indeed, recent evidence from cross-sectional [4] and prospective studies [14, 16–18] supports the adoption of a lower AER cut-off point for the detection of enhanced cardiovascular risk in individuals with arterial hypertension. This probably reflects the fact that microalbuminuria was originally defined on the basis of increased risk for developing diabetic nephropathy. It is now clear that its significance extends beyond nephropathy and it likely mirrors a more widespread vascular injury [33].

The present study was designed to determine whether or not an association between albuminuria and aortic PWV exists, but it does not provide information on the mechanisms of this relationship. Since both microalbuminuria and aortic PWV have been associated with endothelial dysfunction and subclinical atherosclerosis, these latter may be the pathophysiological links between AER and impaired aortic compliance. Indeed, there is some evidence suggesting that leakage of albumin through the glomerular membrane is a reflection of a systemic transvascular macromolecular leakage in atherogenesis, where permeability changes occur since the earliest stage as a consequence of damaged vascular endothelium, a structure intimately involved in vascular permeability as well as haemostasis, fibrinolysis and vasomotion [34–35]. This hypothesis is strengthened by the correlations between AER and circulating endothelium-derived factors secreted in greater amounts by injured endothelium, as observed by our group [36] and other investigators [37]. Moreover, previous findings of an association between greater values of AER and increased carotid intima-media thickness [5–6] and between the level of microalbuminuria and the severity of coronary artery disease [9], further corroborate the view according to

which microalbuminuria may be considered as a marker of preclinical or established atherosclerosis.

On the other hand, arterial stiffness may be partly under the functional control of some substances released from the endothelium, above all endogenous nitric oxide [38, 39], as well as being structurally determined. Moreover, several studies have highlighted the associations between aortic PWV, and most cardiovascular risk factors, and established atherosclerosis [19, 40, 41].

Since both aortic distensibility and microalbuminuria have been related with cardiovascular prognosis, the positive and independent correlation between PWV and AER that we observed may account, at least in part, for the respective influence on cardiovascular diseases. Only future longitudinal prospective studies, evaluating both aortic PWV and microalbuminuria, will clarify the independent contribution of each of parameter on cardiovascular morbidity and mortality.

It is well-known that there is a considerable intrapersonal variation of urinary albumin excretion [1]. Therefore, the measurement of only two AER may be a limitation of our study. However, because of regression dilution, this may have caused an underestimation of the existing positive relationship between urinary albumin excretion and PWV. This suggests that the true association between AER and PWV is likely to be even stronger than observed in the present study. Moreover, in several papers [10, 16–18], in which a relationship between AER and cardiovascular damage and prognosis was found, only one or two measurements were performed.

In conclusion, our study, showing a close and independent relationship between AER and carotid-femoral PWV, seems to confirm the concept according to which microalbuminuria represents the early renal manifestation of a generalized vascular dysfunction, and therefore it is an integrated marker of cardiovascular risk.

Conflict of interest statement

No conflict of interest was declared.

Acknowledgements

This work was supported in part by a grant from the Italian Ministry for University and Scientific Research (MURST). Authors express gratitude to

Mr Giuseppe Patricolo and Mrs Concetta Truscello for their nursing assistance.

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Correspondence: Giuseppe Mulè MD, Via Monte San Calogero, 29, 90146 Palermo, Italy.
(fax: 91-6554331; e-mail: giusemme@email.it)