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Dynamic Measurement and Functional Assessment of $tcpO_2$ and $tcpCO_2$ in Peripheral Arterial Disease

GIUSEPPE M. ANDREOZZI

ABSTRACT

Transcutaneous measurement of pO_2 and pCO_2 has been done since 1974. It was first used to monitor respiratory balance in premature newborns, providing good correlation ($r = 0.98$) with hemogas analysis data. Further applications were in the fields of anesthesiology and angiology, to assess tissue perfusion measuring transcutaneous pO_2 ($tcpO_2$). This application is based on blood oxygen transport and therefore on the correlation between blood flow and $tcpO_2$. These studies have permitted us to further assess peripheral vascular diseases and show good correlation with angiography, laser Doppler, and clinical behaviors; they also help identify the appropriate level for amputation. Other studies investigated $tcpO_2$ changes during some activation tests, such as treadmill, ischemic stress, and O_2 breathing. The best parameters of this functional asset are the increase in $tcpO_2$ during O_2 breathing, the oxygen reappearance time, the oxygen recovery index, and the half recovery time of $tcpO_2$ after ischemia. $tcpCO_2$ was rather neglected by researchers. The results of our experience can be summarized in two points: (1) measurement of the pathophysiological balance of peripheral arterial disease, finding, at Fontaine's stage 2B, a significant worsening of cellular metabolism, a prelude to critical limb ischemia; and (2) assessment of tissue adaptability to ischemia, measuring $tcpCO_2$ production during ischemia. This last parameter is very important in the prognostic balance. It is able to distinguish patients in whom very low $tcpO_2$ levels (0–5 mm Hg) are sustained by blood flow reduction (unrecoverable) from those in whom the low $tcpO_2$ levels are determined by complete tissue utilization of the oxygen supply.

INTRODUCTION

Transcutaneous measurement of pO_2 and pCO_2 has been performed since 1974 using Clark's platinum electrode for oxygen and a glass pH meter for carbon dioxide. An electrical current is produced by an electrochemical reaction between the O_2 and CO_2 molecules that diffuse through the skin toward the cathode of the sensors. The probes can be separate or assembled (Combi sensor). The recording system is thermostatic. Measurement is usually performed by heating the skin to 44°C, which induces an optimal cutaneous microclimate for gas diffusion through the skin. A more physiologic temperature of 33°C has been suggested during dynamic measurement, but this protocol is not utilized much.[1,2] The variability of mea-

Department of Internal Medicine "A. Francaviglia," Chair of Angiology, School of Medicine, University of Catania, Catania, Italy.

surement is very high; one value is not sufficient; an average value after 5 min of measurement after skin temperature stabilization is needed.[3–5]

The measurement investigated most has been transcutaneous pO_2 ($tcpO_2$) analysis, first used to monitor respiratory balance in premature newborns. With the probe placed on the skin of the subclavian fossa, this technique has shown good correlation ($r = 0.98$) with hemogas analysis.[6]

Further applications have been in the fields of anesthesiology and angiology, to assess tissue perfusion measuring $tcpO_2$. This application is based on blood oxygen transport and, therefore, on the correlation between blood flow and $tcpO_2$. The noninvasiveness, the ease, and the reproducibility of the method allowed us to increase diagnostic sensitivity and increase our pathophysiologic knowledge of peripheral vascular diseases, measuring $tcpO_2$ changes during activation tests.

$tcpCO_2$ measurement has been rather neglected. Our group has been reporting on it since 1986. In our experience assessment of $tcpCO_2$ at the same time as $tcpO_2$, at rest and during the dynamic approach, improves the diagnostic and prognostic value of the method, distinguishing patients in whom very low $tcpO_2$ is sustained by blood flow reduction (unrecoverable patients) from those in whom low $tcpO_2$ levels are determined by complete tissue utilization of the oxygen supply.

RESTING AND TOPOGRAPHICAL ASSESSMENT

$tcpO_2$

Topographical assessment has been one of the first targets of the technique, measuring the $tcpO_2$ at different levels of the lower limbs (leg, calf, foot), and referring the values to the subclavian fossa level of $tcpO_2$, assumed as the systemic blood value.[7–9]

In healthy people the $tcpO_2$ shows an isobaric line around 65–80 mm Hg at each point, which disappears in vascular patients at the second stage of Fontaine's classification. The $tcpO_2$ line shows a decrease from the proximal to the distal points, with a higher slope in more advanced stages (Fig. 1).

These topographycal data have shown a good correlation with continuous wave Doppler, the perfusion pressure index, and angiography, giving a reliable profile of hemodynamic reperfusion downstream of the stenosis or obstruction.[10] The $tcpO_2$, measured at the metatarsus (lower leg point), has shown good correlation with the most important functional parameters of peripheral arterial disease: pain-free walking distance, peak flow of the strain gauge plethysmography, plethysmographic functional reserve, and recovery time after pain claudication.

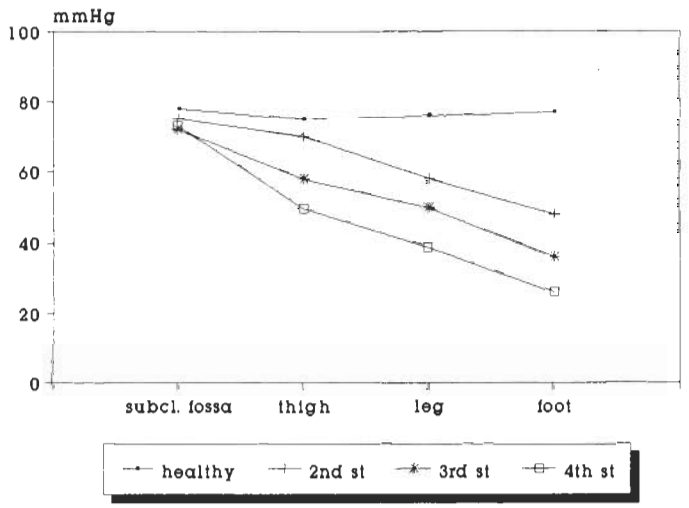

FIG. 1. Topographic assessment of transcutaneous pO_2 in healthy subjects and in patients with peripheral arterial disease.

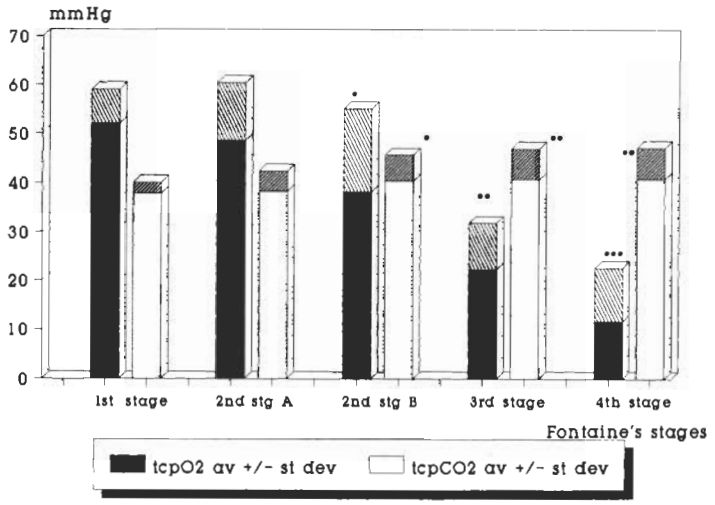

FIG. 2. Metatarsal transcutaneous pO_2 and pCO_2 in patients with peripheral arterial disease. $*p < 0.005$; $**p < 0.001$; $***p < 0.0005$.

On the basis of this good correlation with hemodynamic perfusion data, it has been suggested that the appropriate level for amputation is at the skin point with $tcpO_2$ near 20 mm Hg.[4,5,38] This value indicates the skin point at which good cicatrization would be possible. Amputation may not be indicated each time the $tcpO_2$ is under 20 mm Hg. In fact, $tcpO_2$ values under 20 mm Hg could be found in patients in whom skin perfusion could be restored.[12] There is disagreement on the role of $tcpO_2$ in the determination of the amputation level.[13]

$tcpCO_2$

In spite of its important role, measurement of pCO_2 has received little attention by researchers. In our review of the literature we found several papers about the role of $tcpCO_2$ in clinical pharmacology, hypertension,[14] diabetic microangiopathy,[15] treadmill test,[16] and chronic venous insufficiency.[17] We found few data on the pathophysiologic and diagnostic role of $tcpCO_2$ measurement.

We have been investigating this for a long time and emphasizing its importance in late stages of peripheral arterial disease. In healthy control subjects $tcpCO_2$ levels are within 35–40 mm Hg and the same levels have been measured in stable arteriopathy (Fontaine's stage 2). The decrease in severe tissue ischemia indicates worsening of the cellular metabolism, sustained by a reduction in the responsiviness of oxidative enzymes with lactate production[4] (Fig. 2).

We believe $tcpCO_2$ measurement is very important in these phases. In advanced stages of peripheral arterial disease, in fact, we measured low $tcpO_2$ levels (0–5 mm Hg) in lower limbs that might have been amputated, but that recovered with pharmacological or surgical treatment[3,18–20] (Fig. 3). The low $tcpO_2$ is consequent to a reduction of the O_2 that can pass through the skin. This reduction can be sustained by a decrease in the absolute oxygen in the blood (decrease of the oxygen available, for reduction of blood perfusion) or a relative decrease of oxygen diffusion through the skin by complete utilization of oxygen by the tissues. In these cases the $tcpO_2$ cannot provide correct assessment of the risk of skin necrosis, while $tcpCO_2$ measurement could.

DYNAMIC MEASUREMENTS

The tests most investigated have been the treadmill, the ischemic stress, the postural test, and O_2 breathing.

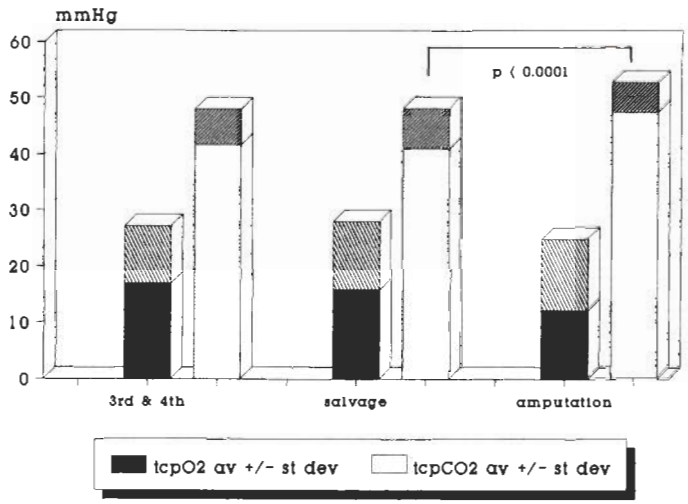

FIG. 3. Metatarsal transcutaneous pO_2 and pCO_2 in patients with peripheral arterial disease.

Treadmill test

The measurement of $tcpO_2$ during muscular exercise with the treadmill test in normal subjects and in the asymptomatic legs of patients with unilateral claudication shows unchanged values.

In patients with claudication $tcpO_2$ maintains baseline levels until pain occurs, when levels became lower. At the end of the exercise $tcpO_2$ falls 27–30% from the resting level.[21–23] During the recovery period $tcpO_2$ decreases again and it reaches the lowest value (47–50% from the baseline) 2.5–4.7 min after exercise stops.[23] This drop in $tcpO_2$ is caused by reduced oxygen delivery to the skin and by increased oxygen extraction from the ischemic muscle.[24] The continuous fall in $tcpO_2$ during the recovery phase is sustained, probably, by maximal oxygen transfer from skin to muscle. Schmidt et al., studying $tcpCO_2$, found a significant difference between patients and controls only during the recovery phase.[16]

$tcpO_2$ level during O_2 breathing

This test measures $tcpO_2$ at rest and after 100% O_2 breathing; the probe is placed at the lower leg point or near the worst skin point. In healthy controls $tcpO_2$ does not change after 100% O_2 breathing, indicating good tissue perfusion. In stable arteriopathy, when $tcpO_2$ is lower than in controls, it increases after O_2 breathing, indicating that perfusion may improve. An increase of at least 10 mm Hg from baseline values, after 6 min of 100% oxygen inhalation, has been found in recoverable patients. Conversely, an increase of less than 10 mm Hg after oxygen breathing has been found in patients undergoing amputation.[4,11]

Postural tests

These tests elicit the baroreceptoral reflex of lower limb microcirculation, known as the antigravity reflex or venoarteriolar reflex (laser Doppler). This reflex in healthy people reduces the arteriolar inflow in an orthostatic position. In patients with peripheral arterial disease this reflex is damaged and the arteriolar vasoconstriction in an orthostatic position is not achievable. $tcpO_2$ in peripheral arterial disease increases more (65% of baseline values) than in healthy controls (16.6%).[40] This assessment improves the diagnostic sensitivity of the method, but postural tests provide more important information with carbon dioxide measurement. Measuring $tcpO_2$ and $tcpCO_2$, Palermo and Allegra found an unfavorable prognosis in patients with a decrease in $tcpO_2$ and an increase in $tcpCO_2$ in a semiorthostatic position, and a favorable prognosis in patients in whom $tcpO_2$ increases and $tcpCO_2$ decreases in this position.[25]

Postischemic tests

Ischemic stress, induced with a cuff inflated to greater than systolic blood pressure and maintained for 3 min, is one of the most frequently used activation tests. It has been proposed that this test be used with $tcpO_2$ assessment, measuring continuously after cuff release. $tcpO_2$ is measured in the supine position, at rest, and during and after 3 min of ischemia. The most used parameters are oxygen reappearance time, oxygen recovery index, half recovery time of $tcpO_2$, and $tcpCO_2$ production during ischemia.

Oxygen reappearance time (ORT) is defined as the time from release of the cuff until $tcpO_2$ starts rising. It is 10–15 sec in healthy controls, 23–65 sec in patients with claudication, and 220–600 sec in critical limb ischemia. When no response to cuff occlusion is observed, the oxygen reappearance time is arbitrarily defined as being equal to 600 sec.[26] Slagsvold et al., simultaneously recording $tcpO_2$ and laser Doppler in healthy controls, found that the laser Doppler signal reappears immediately after cuff release, while the ORT is delayed. This delay is due to the time of oxygen diffusion from the capillaries to the $tcpO_2$ sensor of the probe, through the tissues. This observation confirms that $tcpO_2$ is a "tissue parameter" related to perfusion, but not a perfusion parameter.

In patients with claudication (Fontaine's stage 2A) both parameters are prolonged by a reperfusion delay and by reduced tissue oxygenation. The inhalation of 100% O_2 shortened the ORT but not the laser Doppler reappearance time, confirming the microhemodynamic features of laser Doppler and the tissue features of $tcpO_2$ measurement.

In patients with critical limb ischemia the reappearance of laser Doppler flow and ORT is higher than in healthy controls and patients with claudication; in comparison, the ORT is more prolonged. After 100% O_2 breathing ORT is shortened, but the laser Doppler reappearance time is unchanged, confirming again that ORT is more an index of reduced oxygenation than of delayed reperfusion. Sometimes a shortening of the laser Doppler signal is found, but this is a consequence of the persistence of the response to the previous test, and a longer resting time between dynamic tests is suggested.

Oxygen recovery index (ORI) is defined as the transcutaneous oxygen diffusion rate (kPa/min) at the steepest part of the recovery curve.[26] ORT is 6.4 kPa/min in the healthy controls, 5.1 kPa/min in the patients with claudication, and 0.3 kPa/min in critical limbs ischemia, with no statistical difference between healthy controls and patients with claudication.[27] It was concluded that the healthy controls could have had an asymptomatic atherosclerosis and the patients with claudication could have had good collateralization, to explain the absence of differences between the first and second group. In our opinion, because the ORI is a "functional parameter," this lack of difference means that the compensation mechanisms are still efficient in patients at Fontaine's stage 2A.

After 100% O_2 breathing the ORI increases significantly in all patients, meaning that the red cells are able to deliver additional oxygen despite significantly reduced perfusion. However, this is due to the sigmoidal shape of the Hint's curve and the increase in O_2 extraction in potential ischemic tissue as a result of an increase in regulatory oxidative enzymes. The lower increase of ORI than in controls and claudication patients seems sustained by reduced O_2 delivery through a diminished or absent reactive hyperemia.[27]

Half recovery time of $tcpO_2$ (t/2 $tcpO_2$) is defined as the time needed to recover the half value of the baseline $tcpO_2$ level.[3] In healthy patients the t/2 $tcpO_2$ is less than 60 min, and it becomes gradually longer in different stages of peripheral arterial disease (Fig. 4). The t/2 $tcpO_2$ has shown good correlation with some parameters of functional evaluation of peripheral arterial disease, such as the half time of plethysmographic peak flow and red cell filterability,[28] which are indices of microcirculatory assessment.[29,39] We proposed t/2 $tcpO_2$ as an indirect index of the ability of tissue to regain normal metabolic function. In the diabetic patients, with and without arterial macroangiopathy, we found the t/2 $tcpO_2$ to be longer than in healthy controls. This behavior correlates with the data from other techniques such as laser Doppler, confirming microcirculatory involvement and worse tissue performance in all diabetics, without macrocirculatory arterial disease.[30,31]

$tcpCO_2$ production during ischemia is defined as the increase of $tcpCO_2$ (mm Hg) during 3 min of ischemia, related to the resting value. During ischemia, when $tcpO_2$ falls to zero, $tcpCO_2$ increases. We measure the resting value and value 3 min later, and subtract the first from the second, calculating $tcpCO_2$ production.

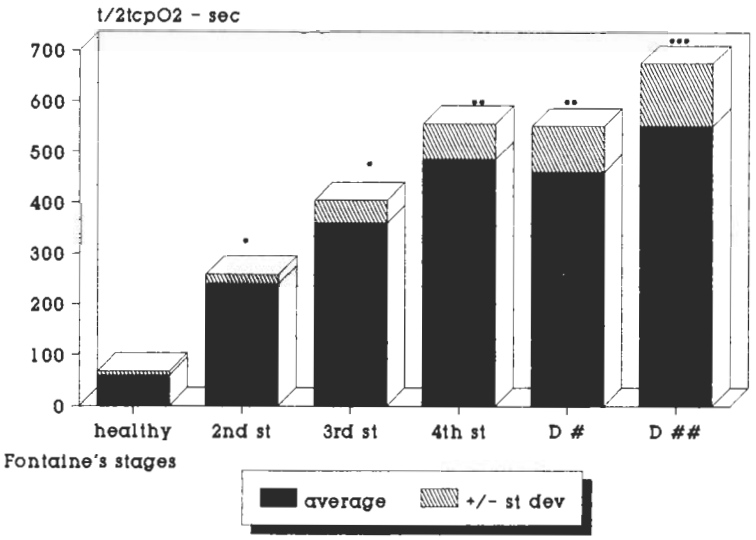

FIG. 4. $tcpO_2$ half recovery time after 3 min of ischemia in patients with peripheral arterial disease and in diabetics with (##) and without (#) arteriopathy. $*p < 0.05$; $**p < 0.005$; $***p < 0.0005$.

Our first observation of parameter was carried out during a study on the efficacy of iloprost on critical limb ischemia. We found that in patients who respond, $tcpCO_2$ production after ischemia was significantly lower than baseline.[32] This result could be assumed to be evidence that the drug can increase tissue tolerance to ischemia in patients with a high grade of arterial obstruction, as previously demonstrated in an experimental study on hypoxia.[33]

We have also been carrying out a retrospective analysis on our data base. We found that resting $tcpCO_2$ increases gradually as the illness worsens. The critical values (42–45 mm Hg) are reached only at stage 4. In the same way $tcpCO_2$ production during ischemia increases, related to the severity of the disease (Table 1).

Stage 2A, the typical stage of arterial insufficiency after muscular stress, shows normal values of resting $tcpCO_2$, with a significant increase during ischemia, but still far from the critical values. In stage 2B the resting $tcpCO_2$ is above 40 mm Hg, and above 45 mm Hg during ischemia (average production 5.22 mm Hg). Stages 3 and 4 show a further increase of $tcpCO_2$ at rest and during ischemia. Only stage 1 shows no significant difference in $tcpCO_2$ production during ischemia, but the trend is clearly similar to the general behavior of the others stages. The lack of significance may be due to the low number of patients observed. We feel that $tcpCO_2$ at rest and during local ischemia might be an important parameter in the evaluation of peripheral arterial disease, better defining the risk of skin necrosis. It could be the expression of tissue metabolic performance and, overall, of tissue resistance to ischemia, while $tcpO_2$ is an expression of tissue perfusion.[20]

TABLE 1. RESTING $tcpCO_2$ AND $tcpCO_2$ PRODUCTION DURING 3 MIN OF ISCHEMIA IN PATIENTS WITH PERIPHERAL ARTERIAL DISEASE

Stage	*Number of patients*	*Resting $tcpCO_2$*	*$tcpCO_2$ during ischemia*	*Average $tcpCO_2$ production*	p <
1	12	37.83 ± 2.25	41.08 ± 8.54	1.09 ± 3.4	n.s.
2A	183	38.32 ± 4.07	42.98 ± 6.14	4.61 ± 1.20	0.0001
2B	194	40.46 ± 5.26	45.70 ± 7.29	5.22 ± 1.70	0.0001
3	83	40.77 ± 6.15	47.11 ± 9.56	6.10 ± 1.50	0.0001
4	53	42.37 ± 6.43	51.02 ± 8.10	8.66 ± 1.90	0.0001

TABLE 2. CORRELATION BETWEEN SOME CLINICAL AND GAS ANALYSIS DATA IN PATIENTS WITH PAIN-FREE WALKING DISTANCE (PFWD) OVER (2A) AND UNDER (2B) 150 mt[a]

	PFWD–tcpO₂	*tcpO₂–tcpCO₂*	*tcpO₂–t/2 tcpO₂*	*tcpCO₂–t/2 tcpO₂*
Stage 2A	0.85	−0.76	−0.79	−0.39
Stage 2B	−0.56	−0.83	−0.64	−0.42
Critical limb ischemia	ND	−0.43	ND	0.64

[a]Analysis of the variance with linear regression test. Stage 2A: good direct correlation between pain-free walking distance and $tcpO_2$ ($r = 0.85$); good inverse correlation between $tcpO_2$ and $tcpCO_2$ and between $tcpO_2$ and t/2 $tcpO_2$; no correlation between $tcpCO_2$ and t/2 $tcpO_2$. Stage 2B: inverse correlation between $tcpO_2$ and pain-free walking distance, higher than 2A; worse inverse correlation between $tcpO_2$ and t/2 $tcpO_2$ than in 2A; algebraic improvement of r between 5/2 $tcpO_2$ and $tcpCO_2$. Critical limb ischemia: no correlation between pain-free walking distance and $tcpO_2$ and between $tcpO_2$ and t/2 $tcpO_2$; poor inverse correlation between $tcpO_2$ and t/2 $tcpO_2$; good direct correlation between $tcpCO_2$ and t/2 $tcpO_2$.

PATHOPHYSIOLOGIC FEATURES

The simultaneous measurement of $tcpO_2$ and $tcpCO_2$ improves the diagnostic ability of the method and increases our knowledge of some interesting pathophysiologic features of peripheral artery disease, emphasizing that the metabolic change, very clear at the stage of the critical limb ischemia, occurs during the stage 2B of Fontaine's classification.

In particular, correlating the metabolic gas analysis pattern with the clinical data, we confirmed that stage 2A is characterized by ischemia related to muscular work, sustained by the oxygen supply during the effort, and critical limb ischemia is characterized by acidosis.

Stage 2B, which has the same clinical handicap as stage 2A, with a difference in the walking distance only, shows a worsening of the aerobic condition of the cellular metabolism, a prelude of critical limb ischemia.[34] We termed this condition unstable arteriopathy, as opposed to the stable condition of stage 2A (Table 2). At stage 2B the pain-free walking distance does not characterize the patients, it is sustained by the adaptation to ischemic work, it changes a lot during the day and the week, and it does not indicate the functional capacity of the patients.[35]

CONCLUSION

We believe that transcutaneous measurement of oxygen and carbon dioxide is, at this moment, one of the best methods to evaluate the microcirculatory and metabolic patterns of peripheral artery disease. Summarizing all the data, we can say that the resting $tcpO_2$ is an expression of arteriolar perfusion, which in peripheral artery disease, depends on the macrocirculatory blood flow; measurement of dynamic parameters such as oxygen recovery time, oxygen recovery index, and half recovery time of $tcpO_2$ after ischemia provides important information about the microcirculatory and metabolic reserve. But it is the resting $tcpCO_2$, and, in particular, $tcpCO_2$ production during ischemia that made it possible to evaluate skin necrosis risk with better accuracy.

This conclusion is not surprising because it has long been known that for nerve cells,[36] all tissues in the human body need more to be free from the carbon dioxide that to obtain the oxygen, in other words, the acidosis is worse than the hypoxia.[37]

ACKNOWLEDGMENTS

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Address reprint requests to:
Dr. G.M. Andreozzi
Department of Internal Medicine "A. Francaviglia"
Chair of Angiology
School of Medicine
University of Catania
Catania, Italy

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