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EDITORIAL

An early proof-of-concept of cardiac resynchronization therapy

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Abstract

Almost 50 years ago, we published detailed hemodynamic findings in a patient with heart failure and intermittent left bundle branch block. Delayed intraventricular conduction was consistently accompanied by an increased duration of left ventricular (LV) isometric contraction, a drop in systolic blood pressure, a rise in heart rate, and a drop in cardiac output. To our knowledge, this observation provided the first ever evidence that delayed mechanical LV contraction was associated with deterioration, and return to a normal pre-ejection phase with improvement in LV function.

Key words: Intermittent left bundle branch bock; Heart failure; Left ventricular dyssynchrony; Systolic blood pressure; Cardiac output

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Almost 50 years ago, one of us (Bourassa MG) co-authored a case report entitled: "Hemodynamic Studies during Intermittent Left Bundle Branch Block"[1]. The patient was a relatively young man with symptoms and signs of heart failure and a heart murmur suggestive of aortic regurgitation. Intermittent left bundle branch block (LBBB) was documented on electrocardiograms (ECG), vectorcardiograms and phonocardiograms prior to cardiac catheterization. During left heart catheterization, the ECG spontaneously changed from a pattern of left ventricular (LV) hypertrophy (QRS duration: 80 ms), to a pattern of LBBB (QRS duration: 160 ms). Following oxygen administration, the ECG rapidly reverted to a pattern of LV hypertrophy with normal conduction. During the procedure, similar ECG sequences occurred during which peripheral, aortic and LV pressure curves were simultaneously recorded and cardiac output was calculated using dye-dilution curves.

Important hemodynamic changes consistently accompanied the occurrence of intermittent LBBB. Notably, systolic pressures in the left ventricle, central aorta and radial artery fell consistently (roughly 20 mmHg during LBBB as compared to normal conduction); cardiac index fell from 2.2 L/min per m^2 during normal conduction to 1.7 L/min per m^2 during LBBB. The ECG showed an immediate increase in heart rate during LBBB, presumably as an attempt to compensate for the decreased cardiac output. Particularly important was the temporal rela-

tionship of cardiac events in both forms of conduction. The time interval between onset of LV depolarization and onset of isometric contraction remained unchanged, and thus, the onset of isometric contraction was not delayed during LBBB. On the other hand, slowing of intraventricular conduction appreciably prolonged the duration of isometric contraction (from 72 ms during normal conduction to 94 ms during LBBB) and, proportionately, of isometric relaxation. Because of prolongation of isometric contraction, both the onset and termination of systolic ejection were delayed during LBBB, although the duration of systolic ejection itself was unchanged. The diastolic period with LBBB was shorter than with normal conduction.

To our knowledge, this observation provided the first ever evidence that slowing of intraventricular conduction and prolonged isometric LV contraction result in decreased force and efficiency of contraction, leading to a notable reduction in cardiac output, a drop in systemic blood pressure and a compensatory increase in heart rate. Conversely, spontaneous or oxygen-induced (in our case) conversion from LBBB to normal LV conduction promptly returned hemodynamic parameters to their previous levels. Thus this severe LV dysfunction was immediately reversible.

LBBB results in a significant delay in aortic opening and closure, but it does not affect the timing of RV events[2,3]. It has been suggested that interventricular dyssynchrony contributes to reduction in the regional ejection fraction (EF) of the septum without impacting LV apical and lateral wall motion[4]. On the other hand, intraventricular dyssynchrony, which is characterized by heterogeneous activation of different LV segments (some being activated early and others late during cardiac contraction), results in decreased cardiac output, systemic blood pressure, maximal rate of pressure rise (dP/dt), and global EF[3,5,6]. Finally, in patients with sinus rhythm, atrial contraction is not followed by a properly timed LV systole and prolonged atrioventricular delay can also contribute to cardiac dysfunction.

In the mid-1990s, some investigators hypothesized that patients with LV dysfunction and delayed intraventricular conduction would benefit from pacing at sites that achieve a more rapid ventricular depolarization and thus a more synchronous contraction[7,8]. This led to evaluation of atrial-synchronized biventricular pacing as a means to resynchronize ventricular contraction and improve cardiac function[7,8]. Cardiac resynchronization therapy (CRT) was shown to improve LVEF and dP/dt, and to reduce LV end-diastolic and end-systolic volumes[9]. Following quite convincing observational data, several large randomized clinical trials demonstrated that multisite ventricular pacing or CRT significantly improved mortality and morbidity in patients with heart failure and complete LBBB[10-14].

Currently, CRT is an established treatment modality for selected patients with systolic heart failure. Selection criteria for implantation of a CRT device include an EF < 35%, NYHA functional class Ⅲ-Ⅳ symptoms, and a wide QRS complex (duration ≥ 120 ms). In patients with mild heart failure, the RAFT study found that CRT provided additional benefit to an implantable defibrillator if intrinsic QRS duration was 150 ms or more[14]. This ECG criterion was incorporated into European guidelines for CRT patients with NYHA class Ⅱ symptoms[15]. Thus, indications continue to expand to less symptomatic patients[14]. However, the intervention is both invasive and costly, and clinical response and long-term outcome are variable. Roughly 30% of patients who meet established criteria do not respond to CRT[7-13,15]. In patients with ischemic cardiomyopathy, Barsheshet *et al*[16] found that those with a QRS duration ≥ 150 ms, blood pressure < 115 mmHg, or LBBB had a more favorable response to CRT with regards to overall mortality or heart failure events. Thus, the subgroup of patients at higher risk for death or heart failure appeared to derive the greatest benefit from CRT. In contrast, identified predictors of a favorable response to CRT in non-ischemic cardiomyopathy were female gender, diabetes, and LBBB[16]. While further studies are required to elucidate pathophysiological mechanisms and clinical implications of such subgroup analyses, current evidence suggests that patients with a wide QRS and RBBB or non-specific intraventricular conduction abnormalities respond less favorably to CRT regardless of the type of cardiomyopathy[17,18].

Predictors of a favorable outcome after CRT include baseline mechanical LV dyssynchrony, optimal LV lead position, and extent and location of myocardial scar[19,20]. However, the pathophysiology of mechanical LV dyssynchrony is complex and both its quantification and the choice of optimal, concordant pacing sites, in the latest mechanically activated region of the LV and remote from an infarct zone, still remain under investigation. The Predictors of Response to CRT trial revealed the technical problems of echocardiographic parameters, such as those derived from M-mode echo, routine pulsed Doppler and tissue Doppler imaging, for predicting response in patients with standard CRT indications[21,22]. More recently, promising new tools such as 2-D speckle tracking and real-time 3D echo, alone or in association with cardiac magnetic resonance imaging, have been shown to improve patient selection for CRT[22]. Other investigators have assessed new lead placement strategies and have concluded that CRT delivered at the optimal LV endocardial sites (sites of latest mechanical activation) is more effective than *via* coronary sinus lead pacing[19,20,23]. Future investigations of epicardial or LV endocardial lead positioning may eventually overcome current anatomical restraints[23].

Finally, it has been shown recently that evidence of mechanical LV dyssynchrony at baseline, usually associated with increased QRS duration, and definite reduction in LV dyssynchrony post-implantation are essential in predicting a positive response to CRT[24]. Our seminal report clearly illustrated the importance of these two mechanisms. Delayed intraventricular contraction was associated with deterioration, and return to a normal pre-

ejection phase was associated with improvement in LV function.

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REVIEW

Near-infrared spectroscopy for evaluation of global and skeletal muscle tissue oxygenation

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Abstract

Non-invasive clinical examination has well-recognized limitations in detecting compensated and uncompensated low flow states and their severity. This paper describes the principles of near-infrared absorption spectroscopy (NIRS) and the basis for its proposed use in heart failure/cardiogenic and septic shock to assess global and regional tissue oxygenation. The vascular occlusion test is explained. Limitations of NIRS, current controversies, and what is necessary in the future to make this technology a part of the initial and ongoing assessment of a patient are also discussed. The ultimate goal of such techniques is to prevent miss-assessment and inadequate resuscitation of patients, two major factors in the development of multisystem organ failure and death.

Key words: Shock; Heart failure; Skeletal muscle; Near-infrared spectroscopy

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INTRODUCTION

The primary task of the cardiovascular system is to deliver enough oxygen to meet the metabolic demands of the body. When it fails to satisfy metabolic demands adequately, shock and tissue hypoxia occur. Sustained tissue hypoxia is one of the most important contributory factors in the pathophysiology of organ dysfunction[1]. Therefore, assessment of the adequacy of global systemic and tissue oxygenation in critically ill patients is indispensable in their treatment[2].

Unfortunately, traditional clinical signs of tissue perfusion that have been used over the last century (capillary refilling, mental status, heart rate, pulse pressure, systemic blood pressure and urine output) are now recognized to be limited in their ability to act as sensitive indicators of tissue perfusion[3-5]. Therefore, detection of compensated shock (the most common presentation of shock) remains a serious challenge. Normalization of these traditional clinical indices after initial resuscitation does not exclude ongoing inadequate tissue perfusion[6]. Over the last two decades, an intense search for a more sensitive monitoring technology has continued[7]. The ideal monitoring modality should provide an indication for the treatment of low flow states and should also act as an ideal assessor of the altered state of oxygen delivery at its earliest stage, even before clinical signs are evident.

Maintenance of adequate oxygen delivery (DO_2) is essential to preserve organ function, and sustained low DO_2 is a path to organ failure and death[8,9]. DO_2 does not influence oxygen consumption (VO_2) until it reaches critically low values (DO_{2crit}), when VO_2 starts to decrease.

It is at this point that VO_2 becomes directly dependent on DO_2. Tissue extraction of oxygen cannot be increased further to meet tissue demands, and cells begin to convert to mainly anerobic metabolism, as manifested by significant increases in metabolic byproducts, and other cellular entities reflective of this state, such as lactate, NADH, and reduced cytochrome oxidase. Each individual organ has its own biphasic relationship with differing points of DO_{2crit}, which can vary significantly based on the severity of the insult, the system's metabolic activity, vascular responsiveness to a myriad of mediators, and the type of insult.

Low cardiac output states (cardiogenic, hypovolemic and obstructive types of shock) and anemic and hypoxic hypoxemia are characterized by a decreased DO_2 but preserved oxygen extraction ratio (OER = VO_2/DO_2) so that DO_{2crit} remains normal. In distributive shock (septic shock), the oxygen extraction capability is altered so that the critical OER is typically decreased. These situations are typically associated with an increased DO_{2crit}, and VO_2 can become dependent on DO_2 even when the latter is normal or elevated. Central venous ($S_{cv}O_2$), and mixed venous oxygen saturation (S_vO_2) are used to estimate the OER as an indicator of global tissue oxygenation.

Regional perfusion changes can occur significantly earlier than traditional global indices[10]. Examples of technologies which may take advantage of regional changes, and which may help identify these states, include transcutaneous pO_2 and pCO_2, subcutaneous and interstitial pH, pCO_2, and pO_2 measurements, gastric and sublingual tonometry, and near-infrared absorption spectroscopy (NIRS)[11].

The technique of NIRS is exciting because it potentially provides noninvasively-derived information concerning all of the major components of oxygen transport, ranging from bulk transport of oxygen to its cellular utilization at the level of the mitochondria. This paper will review the principles of NIRS and its application in assessing global systemic and tissue (skeletal muscle) oxygenation in heart failure/cardiogenic shock and septic shock.

PRINCIPLES OF NEAR INFRARED SPECTROSCOPY

NIRS research for measuring tissue properties is not new[11]. The technique was pioneered by Millikan who developed a dual wavelength oximeter for muscle, and Jobsis who was the first to note the differential spectral absorption of hemoglobin (Hb) and the mitochondrial enzyme cytochrome oxidase or cytochrome a, a3 (CtOx) *in vivo* with NIR transillumination[12,13]. Visible light (450-700 nm) penetrates tissue only a short distance because of strong attenuation by various tissue components. In the NIR spectrum (700-1100 nm), however, photons are capable of deeper penetration (several centimeters or more), even through bone. It is also within this spectral region that oxygen-dependent electronic transitions of the metalloproteins Hb, myoglobin and CtOx can be detected. These metalloproteins act as chromophores and absorb NIR radiation differently based on their concentration and interaction with oxygen. The Beer-Lambert law provides the physical and mathematical basis for NIRS. This law states that light passing through a solution of a colored compound (chromophore) is absorbed by the compound, resulting in a reduction in the intensity of the emerging light[14].

It should be noted now that NIRS differs from pulse oximetry in several important ways. These include the use of different (red) and fewer wavelengths of light in pulse oximetry and the need for pulsatile flow in pulse oximetry. Pulse oximetry is based on the assumption that the only pulsatile absorbance between the photodetector and light source is arterial blood.

HEMOGLOBIN

It is the electronic transition of the heme molecule of Hb and its response to the presence of oxygen that is responsible for its differential absorption of NIR radiation.

The basis for the use of NIRS to monitor changes in Hb and HbO_2 to monitor states of tissue oxygenation lies in the tissue compartmentalization of blood volume, which in most organ systems is believed to be in a ratio of 10:20:70 among the arteriolar, capillary, and venular compartments, respectively[15,16]. Consequently, the majority of the NIRS signal is believed to reflect the venous or post-extraction compartment of any particular tissue. This phenomenon provides valuable information on the tissue oxygen consumption or extraction in much the same way as mixed venous Hb oximetry is used with the pulmonary artery catheter. The NIR value of Hb oxygen saturation from the tissue (StO_2) thus represents spatially integrated information from arterioles, capillaries, and venules, which are normally weighted towards the venous compartment. Larger vessels (> 1 mm) are assumed to be excluded from StO_2 determination[17].

CYTOCHROME OXIDASE

Mitochondrial cytochrome oxidase (CtOx) is responsible for more than 90% of cellular oxygen consumption (reduction) in its role in producing ATP. Although the enzyme contains four metal centers (CuA, heme a, CuB, and heme a3), it is the CuA center that has the strongest absorbance in the NIR region (830 nm), and is responsible for over 80% of the spectral changes in this region[18]. CuA is a unique Cu-Cu dimer, which is a one-electron acceptor - a donor that accepts an electron from cytochrome c and mediates its transfer[18]. Hb NIR absorbance is directly proportional to oxygen binding to its metal centers, but NIR changes in the CtOx signal are due to a decrease in electron flow, a consequence of insufficient oxygen in the environment. Reduction of CtOx results in the disappearance of its 830 nm absorption band. These facts are largely responsible for the signifi-

cant challenges in monitoring and quantifying changes in the CtOx redox state, except from a baseline state. This overall absorption signal will represent only the immediate steady-state contribution of both the oxidized and reduced form of the enzyme within the volume of tissue being sampled, but again, can only be compared with the changes preceding or following it (trend monitoring) without knowing if the baseline state was normal to begin with. Thus to date, it has only been possible to calculate the percentage of the oxidized *vs* reduced form of the enzyme in animal models where the enzyme is transiently totally reduced (anoxia), the total enzyme concentration is known, and the optical path length is measured. More NIRS studies coupled with the use of nuclear magnetic resonance (which can determine the onset of intracellular dysoxia and the oxygenation status of Hb and myoglobin) should be performed to enhance our understanding of the ability of NIRS to accurately perform as a precise monitor of tissue oxygen transport[19].

CLINICAL EVALUATION

The use of NIRS is an attempt to move beyond the common physical examination in order to avoid tissue dysoxia. Thus, determination of regional StO_2 might provide an early warning of global hypoperfusion prior to significant alterations in vital signs or DO_{2crit}. Additionally, it would allow clinicians to guide resuscitations better and reduce periods with occult tissue hypoxia. Changes in StO_2 would provide an earlier warning sign of impending dysoxia and would help the clinician ensure that oxygen delivery to the tissue had been restored to a level well above that required to simply reverse dysoxia. However, it may not be obvious of what value the monitoring of the CtOx redox state should be. As expected, the regional CtOx redox state has been shown to correlate strongly with regional VO_2 ($r^2 = 0.9$) only when VO_2 becomes dependent on DO_2 (below DO_{2crit})[20]. When both StO_2 and CtOx redox statuses have been studied together in organs not containing myoglobin, changes in StO_2 occurred first in response to reductions in DO_2, and were restored last on restitution of regional DO_2[21].

NIRS OF SKELETAL MUSCLE IN HEART FAILURE AND CARDIOGENIC SHOCK WITH OR WITHOUT SEVERE SEPSIS/ SEPTIC SHOCK

Measurement of SvO_2 from the pulmonary artery is used for calculations of oxygen consumption and has been advocated as an indirect index of tissue oxygenation and a prognostic predictor in critically ill patients[22-25]. However, catheterization of the pulmonary artery is costly, has inherent risks and its usefulness remains under debate[26,27]. In a recently published paper, we studied skeletal muscle StO_2 in severe left heart failure with or without additional severe sepsis/septic shock, and compared it with SvO_2[28].

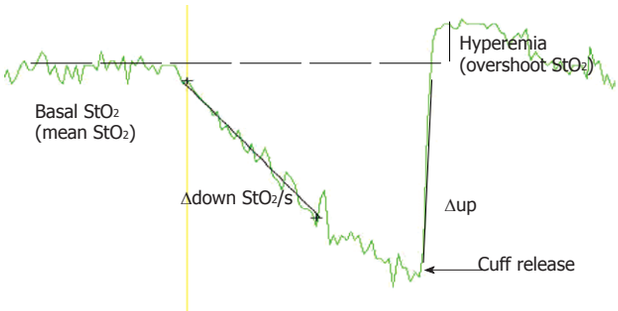

Figure 1 Vascular occlusion test: An original thenar tissue oxygen saturation (StO_2) recording after arterial upper arm cuffing, and cuffing release (upper arm ischemia reperfusion test). During the upper arm ischemia reperfusion test, several StO_2 parameters can be studied: average StO_2 before arterial cuffing/occlusion; StO_2 downslope during cuffing-the deoxygenation rate (Δdown StO_2)/s); StO_2 upslope (Δup StO_2)/s); hyperemia (overshoot of StO_2 above baseline).

The hypothesis was that skeletal muscle StO_2 could estimate SvO_2 in patients with severe left heart failure and preserved oxygen extraction capability (without severe sepsis/septic shock), because blood flowing through upper limb muscles could make an important contribution to flow through the superior vena cava. On the other hand, in patients with a decreased oxygen extraction capability (with severe sepsis/septic shock), we expected disagreement between StO_2 and SvO_2, because in these patients, higher oxygen extraction can probably take place in other organs different from skeletal muscles.

The results confirmed the hypothesis that skeletal muscle StO_2 does not estimate SvO_2 in patients with severe left heart failure and additional severe sepsis or septic shock. However, in patients with severe left heart failure without additional severe sepsis or septic shock, StO_2 values could be used for fast non-invasive SvO_2 estimation; and the trend of StO_2 may be substituted for the trend of SvO_2. The results were in concordance with our previous report of high StO_2 and the slow deceleration rate of StO_2 during stagnant ischemia in septic patients[29]. In this study we used the vascular occlusion test to study dynamic changes in skeletal muscle StO_2. Upper limb ischemia was induced by rapid automatic pneumatic cuff inflation around the upper arm (Figure 1). During the vascular occlusion test, several StO_2 parameters can be studied: mean StO_2 before arterial cuffing/occlusion; StO_2 downslope during cuffing-the deoxygenation rate (Δdown StO_2/s); StO_2 upslope (Δup StO_2/s); hyperemia (overshoot of StO_2 above baseline). The deoxygenation rate is a surrogate for tissue oxygen consumption.

Our group confirmed that thenar muscle tissue deoxygenation during stagnant ischemia at admission and after hemodynamic stabilization was significantly slower in septic shock compared with that in severe sepsis, localized infection and healthy controls. The rate of StO_2 decrease correlated strongly with the severity of septic shock (Sequential Organ Failure Assessment score) and weakly with norepinephrine requirement, plasma lactate and C-reactive protein concentrations. The muscle tissue

deoxygenation rate increased with improvement in sepsis in the septic shock and severe sepsis group.

Our results were in accordance with those reported in a baboon septic shock model[30]. In these primates, the NIRS-determined rate of skeletal muscle enzyme CtOx a, a3 reduction during stagnant ischemia was decreased in Gram-negative septic shock. These data were interpreted as being consistent with the presence of a defect in the ability of the enzyme to accept electrons from oxygen or a limitation in the availability of the reducing equivalent. Similar results were reported in the dog gracilis muscle preparation after treating the animals with endotoxin[31].

The high StO_2/low SvO_2 seen in severe sepsis and septic shock, suggest blood flow redistribution. Thenar muscle StO_2 probably correlates with $ScvO_2$ which is measured in the mixture of blood from head and both arms. In healthy resting individuals $ScvO_2$ is slightly lower than SvO_2[32]. Blood in the inferior vena cava has a high oxygen content because the kidneys do not utilize much oxygen but receive a high proportion of the cardiac output[33]. As a result, inferior vena cava blood has a higher oxygen content than blood from the upper body, and SvO_2 is greater than $ScvO_2$.

This relationship changes in periods of cardiovascular instability. Scheinman and co-workers performed the earliest comparison of $ScvO_2$ and SvO_2 in both hemodynamically stable and shocked patients[34]. In stable patients, $ScvO_2$ was similar to SvO_2. In patients with a failing heart, $ScvO_2$ was higher than SvO_2, and in patients with shock the ratio of SvO_2 to $ScvO_2$ was greater (47.5% ± 15.11% *vs* 58.0% ± 13.05%, respectively, $P < 0.001$). Lee and co-workers described similar findings[35]. Other more detailed studies in mixed groups of critically-ill patients designed to test if the $ScvO_2$ measurements could substitute for SvO_2 showed problematically large confidence limits[36], and poor correlations between the two values[37].

Most writers attributed this pattern to changes in the distribution of cardiac output that occur in periods of hemodynamic instability. In shock states, blood flow to the splanchnic and renal circulations drops, while the flow to the heart and brain is maintained[38]. This results in a drop in oxygen content of blood in the inferior vena cava. As a consequence, in shock states the normal relationship is reversed and $ScvO_2$ is greater than SvO_2[34-36]. Consequently, when using $ScvO_2$ or probably StO_2, as a treatment goal, relative oxygen consumption of the superior vena cava system may remain stable at a time when oxidative metabolism of vital organs, such as the splanchnic region, may reach a level where flow-limited oxygen consumption is achieved, together with a marked decrease in oxygen saturation. In this situation, StO_2 provides a false favorable impression of adequate body perfusion, because of the inability to detect organ ischemia in the lower part of the body. A recent paper confirmed our hypothesis of the relationship between StO_2 and invasive oxygen delivery measurements in early under-resuscitated septic shock[39].

The hypothesis that the skeletal muscle StO_2 deoxygenation rate correlates (or is inversely proportional) to the $ScvO_2$-SvO_2 difference in patients with severe heart failure with additional sepsis/septic shock was confirmed by our recent study[40]. We also showed that these patients had a clinically considerable $ScvO_2$-SvO_2 discrepancy. Monitoring $ScvO_2$ is a simpler and cheaper method of assessing the global DO_2 to oxygen consumption ratio, but its use as a treatment monitor in patients with severe heart failure with additional sepsis/septic shock is questionable.

Our data in patients with severe heart failure/cardiogenic shock without severe sepsis/septic shock are supported by previous work of Boekstegers *et al*[41], who measured the oxygen partial pressure distribution in the biceps muscle. They found low peripheral oxygen availability in cardiogenic shock compared with sepsis. In cardiogenic shock, skeletal muscle oxygen partial pressure correlated with systemic oxygen delivery ($r = 0.59$, $P < 0.001$) and systemic vascular resistance ($r = 0.74$, $P < 0.001$). No correlation was found between systemic oxygen transport variables and skeletal muscle partial oxygen pressure in septic patients. These measurements were performed in the most common cardiovascular state of sepsis in contrast to hypodynamic shock, which is only present at the very final stage of sepsis or in patients without adequate volume replacement[42]. In the following study, the same authors showed that even in the final state of hypodynamic septic shock, leading to death, mean muscle partial oxygen pressure did not decrease to < 4.0 kPa before a circulatory standstill[41].

In a human validation study, a significant correlation between NIRS-measured StO_2 and venous oxygen saturation ($r = 0.92$, $P < 0.05$) was reported, where the venous effluent was obtained from a deep forearm vein that drained the exercising muscle[43]. StO_2 was minimally affected by skin blood flow. Changes in limb perfusion affect StO_2: skeletal muscle StO_2 decreases during norepinephrine infusion and increases during nitroprusside infusion.

StO_2 overestimated SvO_2 (bias -2.5%) in severe heart failure without severe sepsis/septic shock in our study[28]. This may be due to the NIRS method, which does not discriminate between compartments. It provides a global assessment of oxygenation in all vascular compartments (arterial, venous and capillary) in the sample volume of underlining tissue. The non-invasive measurement of only venous oxygen saturation is complicated by the fact that the isolation of the contribution of the venous compartment to the non-invasive optical signal is not straightforward. New methods, such as NIR spiroximetry, which measures venous oxygen saturation in tissue from the NIR spectrum of the amplitude of respiration-induced absorption oscillations, may lead to the design of a non-invasive optical instrument capable of providing simultaneous and real-time measurements of local arterial, tissue and venous oxygen saturation[1].

In low flow states such as heart failure/cardiogenic

shock, where there are still controversies on how to monitor them[45], it appears logical to combine data of both macro- and micro-circulation parameters to guide resuscitation[46]. A large prospective study is being performed now to evaluate the possibility of additional StO_2 regional monitoring for tissue oxygenation guidance on top of the early goal directed therapy suggested by Rivers *et al*[47].

CONCLUSION

The present review provides a foundation to understand and evaluate the potential value and limitations of NIRS as a tool in the assessment of critically ill patients. Despite continuing technical controversies concerning signal derivation, accuracy, precision, and quantitative ability, skeletal muscle NIRS clearly demonstrates promise in being able to monitor the balance of oxygen delivery and consumption at the end-organ level in severe heart failure or cardiogenic shock. It is also possible to estimate global oxygenation in low cardiac output states without additional severe sepsis or septic shock. However, a significant amount of additional work may be required to determine: (1) the contribution of myoglobin to the StO_2 signal in humans, if skeletal muscle is the end-organ being monitored; (2) quantification of the CtOx redox signal; (3) definitive determination of the etiology of decoupling of the StO2 and CtOx redox NIRS signals in multisystem organ failure; (4) interpretation of the ischemia reperfusion test; and (5) assessment of whether there are significant advantages in monitoring one organ system over another in cases of shock. Many of these issues should be addressed before NIRS comes into widespread use as a tool in the initial evaluation and treatment of these severely ill patients.

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BRIEF ARTICLE

Cardiovascular disease research in Latin America: A comparative bibliometric analysis

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Abstract

AIM: To investigate the number of publications in cardiovascular disease (CVD) in Latin America and the Caribbean over the last decade.

METHODS: We performed a bibliometric analysis in PubMed from 2001 to 2010 for Latin America and the Caribbean, the United States, Canada, Europe, China, and India.

RESULTS: Latin America published 4% of articles compared with 26% from the United States/Canada and 42% from Europe. In CVD, Latin America published 4% of articles *vs* 23% from the United States/Canada and 40% from Europe. The number of publications in CVD in Latin America increased from 41 in 2001 to 726 in 2010.

CONCLUSION: Latin America, while publishing more articles than previously, lags behind developed countries. Further advances in research infrastructure are necessary to develop prevention strategies for this region.

INTRODUCTION

Over the last half century chronic diseases have steadily increased, accounting for 60% of the estimated 58 million people who died globally in 2005[1]. By 2030 this number is expected to increase to 69% of all deaths, partially due to a combination of increased life spans and improvement in infectious disease control[2-6]. With the majority of these deaths expected to occur in low-income and middle-income countries, chronic diseases are changing from being a problem in rich countries to the main crisis in poor countries[6]. This shift is also due to the steady decrease in certain chronic disease deaths, such as cardiovascular disease (CVD), in developed countries[7-9]. Despite this projection, it has been proposed that by decreasing the death rates from chronic diseases by 2% a year, 36 million deaths could be prevented by 2015[10].

Latin America remains one of the regions with high CV mortality rates despite advances in overall development[11]. Out of all Latin American countries only Argentina, which had high mortality rates in the 1970s, has

seen a decline similar to those reported in North America (-63% between 1970-1972 and 1998-2000 in Argentina, Canada, and the United States)[11]. Despite this decline, the absolute mortality rates remain higher in Argentina compared to the United States and Canada[12]. Declines have been smaller in other countries in the region such as Brazil, Chile, and Cuba (-18%, -33% and -2%, respectively)[11]. While in recent years the rates have varied less in countries in the region, it is estimated that mortality due to CVD and stroke in Latin America will increase by 145% among men and women from 1990 to 2020 as compared to only a 28% increase for women and a 50% increase for men over the same period in developed countries[11,13].

Taking into account this increasing CVD burden, we tried to ascertain the current level of CVD research in Latin America and the Caribbean (LA&C) and whether it reflected the magnitude and extent of this epidemic, through a bibliometric analysis in PubMed. We then further evaluated the number of publications in LA&C compared to the United States, Canada, and all European countries including Russia, Western Europe, China and India.

MATERIALS AND METHODS

We performed a bibliometric analysis of the National Library of Medicine and the National Institute of Health PubMed database (Bethesda, MD, United States) to describe the number of publications from LA&C during 2001-2010 on May 23, 2011. Limiting our search criteria to the years 2001-2010, we searched PubMed using MeSH terms for: (1) LA&C; (2) United States and Canada; (3) all Europe including Russia; (Table 1); (4) Western Europe; (5) China; (6) India; (7) Argentina; (8) Brazil; (9) Chile; (10) Colombia; (11) Mexico; (12) CVD, including hypertension and cerebrovascular disease; and (13) clinical, epidemiological, and public health studies articles (Appendix A available online). We then searched for studies in CVD by region and specific countries by combining MeSH terms for each region and CVDs (individually combining strategies #1-11 + #12). We assessed the total number of articles on clinical, epidemiological, and public health studies by region and country (individually combining strategies #1-11 + #13), and clinical, epidemiological, and public health studies on CVDs by region and country (individually combining strategies #1-11 + #12 + #13) (Appendix A). Finally, we evaluated the number of publications in 2001 *vs* 2010 by region, for total publications (strategies #1-6) and in CVDs (individually combining strategies #1-6 + #12).

Table 1 European countries included in the PubMed database analysis performed February 2011

Western Europe	Eastern Europe and Russia
Andorra	Albania
Austria	Armenia
Belgium	Azerbaijan
Cyprus	Bosnia-Herzegovina
Denmark	Bulgaria
Finland	Croatia
France	Czech Republic
Germany	Estonia
Gibraltar	Hungary
Great Britain	Latvia
Greece	Lithuania
Iceland	Moldova
Ireland	Montenegro
Italy	Poland
Liechtenstein	Republic of Belarus
Luxembourg	Republic of Georgia
Malta	Republic of Macedonia
Monaco	Romania
Netherlands	Russia
Norway	Serbia
Portugal	Slovakia
San Marino	Slovenia
Scotland	Ukraine
Spain	Yugoslavia
Sweden	
Switzerland	
Wales	

RESULTS

From January 2001 through December 2010 approximately 6.7 million articles were published in PubMed worldwide. Articles from LA&C accounted for 3.63% of the total publications (243 983 publications), and of these almost 80% came from three countries: Argentina, Brazil and Mexico (Table 2). This compared with 41.56% from Europe and 26.28% from the United States and Canada. Of the articles published from Europe, the majority came from Western Europe (2 771 953 articles of the 2 798 988 total articles). China and Indian subcontinents produced 5.73% and 2.54% of the total articles, respectively. When adjusting the number of publications by population, Western Europe produced the most articles (6679 publications/1 million persons) while India produced the least (144 publications/1 million persons). The top four Latin American countries, Argentina, Brazil, Mexico, and Chile, individually produced more articles when adjusted for population than China or India (600, 574, 414 and 728 *vs* 287 and 144, respectively, per million population). Interestingly Chile, which produced little more than 5% of the total publications in LA&C, had the highest population-adjusted publication rate of the region (728 publications/million persons).

Regarding clinical, epidemiological, and public health publications worldwide, out of 283 900 articles, the United States/Canada produced 24.6% (69 844 articles) of the total, while China produced 9.63% (27 337 articles). Europe, LA&C and India published roughly the same number of articles (15 141, 12 104 and 12 469 articles, respectively).

Worldwide, in 2001-2010 there were 32 833 publications that focused on CVD. Of these, 4.08% (1338 publications) were performed in LA&C, with Argentina, Brazil and Mexico again being the largest producers (Table 2). China produced 10.65% (3499 publications) and India

Table 2 Publications in Medline and Pubmed, 2001-2010[1]

All publications	Population[2]	Publications	Publications/million persons	World total (%)
Worldwide	6920	6734804	973	100.00
China	1344	385614	287	5.73
India	1189	171083	144	2.54
All Europe + Russia	857	2798988	3266	41.56
All of LA&C	597	243983	408	3.63
Western Europe	415	2771953	6679	41.15
United States and Canada	347	1770046	5100	26.28
Brazil	203	116535	574	1.73
Mexico	114	47180	414	0.70
Colombia	45	5943	132	0.09
Argentina	42	25180	600	0.37
Chile	17	12370	728	0.18
Cardiovascular diseases				
Worldwide	6920	32833	4.8	100.00
China	1344	3499	2.6	10.65
India	1189	1294	1.1	3.94
All Europe + Russia	857	12985	15.2	39.55
All of LA&C	597	1338	2.2	4.08
Western Europe	415	12655	30.5	38.54
United States and Canada	347	7613	21.9	23.19
Brazil	203	815	4.0	2.48
Mexico	114	164	1.4	0.50
Colombia	45	29	0.7	0.09
Argentina	42	105	2.5	0.32
Chile	17	69	4.1	0.21

LA&C: Latin America and the Caribbean. [1]Accessed February 2011; [2]2011 estimates in millions[31].

3.94% (1294 publications), while the United States/Canada produced 23.19% (7613 publications) and Europe 39.55% (12985 publications of which 12655 were from Western Europe). The number of articles varied markedly by country with Brazil producing approximately five times as many articles on CVDs than Mexico, the country with the second highest publication rate (815 and 164 articles, respectively). However, when adjusted for population, Brazil and Chile produced the highest number of publications (4 and 4.1, respectively, per 1 million population) in LA&C. Brazil and Chile also produced more publications per million people than China or India (2.6 and 1.1, respectively) but far less than the United States/Canada and Western Europe (21.9 and 30.5, respectively). Finally, approximately half of the articles published about CVDs were clinical, epidemiological, and public health papers regardless of the region (1338 articles in LA&C; 3436 articles in the United States and Canada; 6320 articles in Europe, 1211 articles in China, and 691 articles in India).

When evaluating the trend of total publications produced in 2001 *vs* 2010 in LA&C, the number has doubled (15939 in 2001 to 36978 in 2010). CVD publications also increased substantially from 2001 compared with 2010 (41 *vs* 726) in LA&C. This increase in total publications was also seen in the other regions, with the United States/Canada increasing publications from 150705 to 229911, in Europe from 215401 to 409258 (Western Europe 213024 to 405898), in China from 15888 to 74613, and in India from 10976 to 28635.

DISCUSSION

This bibliometric analysis describes the trend in scientific publications in LA&C, highlighting the increase in articles published over the last 10 years, particularly in CVD research. Although the number of publications remain less than 5% of all articles, there is a reassuring trend which may be due to various factors including global attention on the impact of non-communicable diseases in developing countries, increased support from national public funding agencies resulting from a local shift in the political agenda of Latin American countries, and improvement in support from other international agencies[10,11,14-18]. Furthermore, we did not take into account the impact factor of the publications, which may have widened the gap of CVD publications between developing and developed countries and regions.

Some of the recent increase may be due to the establishment of research centers such as the Collaborating Centers of Excellence which have been established with support from the National Heart, Lung, and Blood Institute with the goal of conducting research to improve the prevention and management of chronic CVDs[18]. Four of these sites are in Latin America and have already begun epidemiological research investigations such as the Centro de Excelencia en Salud Cardiovascular para el Cono Sur[19]. These centers allow for further infrastructure development and planning, furthering the research needs of Latin America.

Insufficient research funding and infrastructure are some of the largest limitations in performing and publishing research in Latin America. While agencies such as the National Institutes of Health are allocating more resources for research, the reality for local and national governments in most Latin American countries involves issues such as healthcare access and coverage, not mentioning education and housing, which are higher national priorities than health research. This is a major difference compared with developed countries such as the United States, that has a human development index of 0.902 (compared with 0.775, 0.750 and 0.699 for Argentina, Brazil, and Mexico, respectively) and is able to focus more resources towards research[20]. For instance, when comparing gross domestic product (GDP) per capita, the United States ($47284 in international dollars) has a higher GDP per capita than Argentina ($15854), Brazil ($11239), or Mexico ($14430), and the percentage of the GDP devoted to research is much higher in the United States (2.67% *vs* 0.51%, 1.02% and 0.5%, respectively)[21,22]. Funding is not the only issue. Another limitation is the poorly developed research network and capacity with few mentors available for training young investigators as well as no established academic career structure. These limitations are slowly being overcome with institutions such as some Centers of Excellence that have set training and infrastructure building as priorities[23]. Finally, Latin American authors may be limited in publishing in

English language journals because of both a language barrier and an element of bias from journals for research that has been generated in developing countries[23].

Unlike medical teaching and skills which can help serve a small community, research leads to programs that can influence populations on a wide level, influence change at a policy level, and be applied to entire populations. Therefore, data management and research are needed as part of a multi-factorial approach to effectively control chronic diseases by improving local data acquisition, and defining resource needs in resource-limited areas, and to assess what programs work in different settings. Thus, evidence-based approaches should be the basis of all actions to ensure that the resources being devoted to a program are effectively working in the community to impact on chronic diseases[24]. There are certain steps that Latin America should take to continue improving its research capability. Initially, development of the research infrastructure and capacity needs to occur as it has been argued that strengthening research capacity is one of the most powerful, cost-effective, and sustainable means of advancing health and development[25]. Infrastructure building can be facilitated by financial, political, and resource support from both local governments, regional health agencies such as the Pan American Health Organization, and local and foreign agencies such as the Global Alliance for Chronic Disease, which combines six of the world's foremost public health research funders (United States, United Kingdom, Canada, Australia, China and India) to fund implementation research on non-communicable diseases in developing countries[26]. Furthermore, institutions should focus on developing a career track for researchers and building mentor-mentee relationships to train young investigators. Institutional mission statements need to be developed with a focus on research and training goals as well as a strong focus on national healthcare priorities. By allocating their resources towards national health priorities, Latin American institutions can improve funding while applying research-based evidence that optimizes health benefits for their community. The success of this strategy is based on a belief that, with increased local political will, further investments can be obtained, and both of these are needed to establish an effective, sustainable, and productive research community.

Local and national support can be gained by tailoring research to the needs of the particular population as well as the priorities set in the policy agenda. These agendas should be long-term plans with sustained and reliable investment[25]. This tailored research plan is important as the habits and prevalence of risk factors can differ not only between countries within a region, but also within cities or social classes[27-30]. Therefore, epidemiologic research focusing on area-specific needs to assess the burden of disease and to identify potential prevention strategies, such as community-based interventions or lifestyle changes can lead to the support of local and national organizations. Once this has been identified, research can be focused on translating the research into the best practices and disseminating the knowledge amongst governments, universities, and agencies. While it is unclear how teaching and research impacts the prognosis of CVD, by focusing on research, infrastructure building, and disease prevention we will hopefully begin to measure and see improvements in the future of Latin America's health and put a stop to the predicted epidemic.

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COMMENTS

Background

Over the last half century, chronic diseases have steadily increased and cardiovascular disease (CVD) now accounts for 17.7 million annual deaths worldwide, constituting 11% of estimates for the global burden of disease. With increasing life spans and improved infectious disease control, the impact of chronic diseases are estimated to grow to 69% of deaths by 2030, with 80% expected in low-middle income countries. In Latin America the mortality due to CVD and stroke is estimated to increase 145% from 1990 to 2020. Understanding the prevalence of CVD and associated risk factors is key to developing policies to combat these conditions.

Research frontiers

To ensure that measures are taken to improve the future of CVD in Latin America an expansion of research and network building needs to be initiated. Studies focusing on defining the problems and designing cost-effective, high impact strategies are necessary.

Innovations and breakthroughs

Few studies have demonstrated the level of research being produced in Latin America despite the increasing burden of CVD in this area. This study outlines the level of research being produced and provides a comparison amongst highly developed and developing countries.

Applications

By understanding the type and level of research being produced from Latin America, the authors explain how further advances in research infrastructure are necessary to develop prevention strategies for this region.

Terminology

A bibliometric anaylsis is the analysis of a body of literature to reveal the pattern of publications in a field.

Peer review

The authors performed a bibliometric analysis in PubMed from 2001 to 2010 for Latin America and the Caribbean, the United States, Canada, Europe, China, and India. Through this search they discovered that, while interest in chronic diseases have improved, Latin America only produced 4% of chronic disease publications worldwide. While the number of publications in CVD in Latin America has increased significantly over the last 10 years, the studies published have not been population based prospective follow up studies and typically do not

represent countrywide prevalence of disease. These results are interesting and represent areas for potential research focus.

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Cardiology Update: Caribbean Cruise
San Diego, CA, United States

March 25
Cardiology for General Practice
London, United Kingdom

April 1-2
11th Annual Spring Meeting on Cardiovascular Nursing
Brussels, Belgium

April 14-16
EuroPRevent 2011
Genova, Switzerland

April 30-May 4
ATC 2011 - 2011 American Transplant Congress
Philadelphia, United States

May 11-14
3th Radiochemotherapy and Brachitherapy Congress & 6th Medical Physycs Meeting
Córdoba, Argentina

May 15-18
ICNC10 - Nuclear Cardiology and Cardiac CT
Amstedan, The Netherlands

May 19-20
Adult Cardiovascular Pathology
London, United Kingdom

May 20-22
XXIX NATIONAL CARDIOLOGY CONGRESS
Córdoba, Argentina

May 20-22
4th Meeting Uremic Toxins and Cardiovascular Disease
Groningen, The Netherlands

May 21-24
Heart Failure Congress 2011
Gothenburg, Sweden

June 2-5
CODHy 2011 - The 1st Asia Pacific Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension
Shanghai, China

June 26-29
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Madrid, Spain

June 29-July 1
Hands-on Cardiac Morphology - Summer Edition
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ESC 2011 - European Society of Cardiology Congress 2011
Paris, France

October 23-26
9th International Congress on Coronary Artery Disease
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World Journal of Cardiology

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INSTRUCTIONS TO AUTHORS

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Acknowledgments

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2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean ± SD or mean ± SE.

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Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

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Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
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