Biophysical Chemistry 195 (2014) 8–15

Contents lists available at ScienceDirect

Biophysical Chemistry

journal homepage: http://www.elsevier.com/locate/biophyschem

Simulation of blood oxygenation in capillary membrane oxygenators using modified sulfite solution

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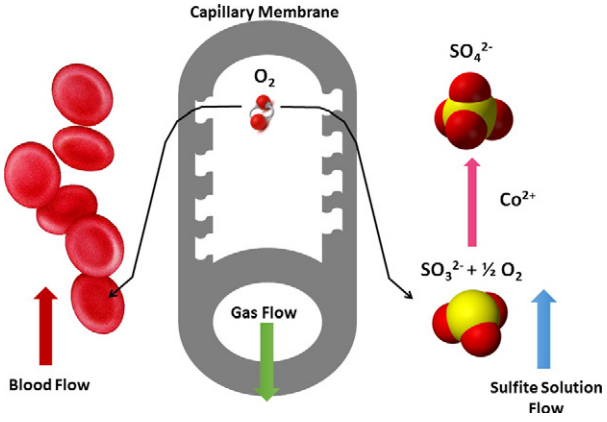
GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 1 July 2014
Accepted 23 July 2014
Available online 7 August 2014

Keywords:
Oxygen transfer rate
Capillary membrane oxygenator
Sulfite solution
Blood oxygenation
Simulation

ABSTRACT

Blood oxygenation is the main performance characteristic of capillary membrane oxygenators (CMOs). Handling of natural blood in in vitro investigations of CMOs is quite complex and time-consuming. Since the conventional blood analog fluids (e.g. water/glycerol) lack a substance with an affinity to capture oxygen comparable to hemoglobin's affinity, in this study a novel approach using modified sulfite solution is proposed to address this challenge. The solution comprises sodium sulfite as a component, simulating the role of hemoglobin in blood oxygenation. This approach is validated by *OTR* (oxygen transfer rate) measured using native porcine blood, in two types of commercially available CMOs. Consequently, the number of complicated natural blood investigations in the evolution procedure of newly developed oxygenators would considerably decrease. Moreover, the reassessing of failed devices, in clinics, would be performed more precisely using a modified sulfite solution than simple water/glycerol testing.

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http://dx.doi.org/10.1016/j.bpc.2014.07.005
0301-4622/

1. Introduction

An oxygenator is a vital instrument, which substitutes the role of natural lung, in some critical extracorporeal applications, e.g. cardiopulmonary bypass surgeries [1,2]. Oxygen transfer rate is a major parameter evaluating the efficacy of an oxygenator [3,4]. In conventional investigations of *OTR* in oxygenators, natural human or animal blood is used [5]. However, the application of natural blood accompanies a lot of handling difficulties [6]. On the one hand, safety is a serious problem since human or animal blood may cause zoonotic or transmissible diseases. On the other hand, blood should be fresh, anti-coagulated (adding heparin, EDTA, citrate, etc.), and specifically prepared for each experimentation. For example, to investigate the *OTR* of a membrane oxygenator in vitro, blood parameters ought to be set to that of mixed venous blood requiring a complex preprocessing of blood through a deoxygenating circuit [7,8].

Considering blood nature, there are many factors affecting the blood's O_2 uptake (e.g. *Hct*, *BE*, p_{O_2}, p_{CO_2}). In this regard, global standard organizations such as FDA defined an almost wide range of fluctuations for the blood inlet parameters for the investigations of oxygenators' performance characteristics. This standard is known as DIN EN ISO 7199 for blood gas exchangers provided by the Association for the Advancement of Medical Instrumentation (AAMI). Table 1 shows general specifications for inlet blood based on the AAMI standard [9–13].

It is obvious that the reproducibility of in vitro studies with natural blood is challenging [14–17]. In addition, such investigations necessitate the use of different specific devices, such as blood gas analyzer and blood pressure sensors, to measure the blood parameters [18,19]. All these obstacles corroborate the need for a simple, straightforward and widely available alternative approach to measure blood oxygenation through membrane oxygenators.

Commonly, distilled and deionized water has been used as an alternative to blood in the gas exchange experiments of CMOs [20]. However, the Newtonian behavior of water, in contrast with the non-Newtonian behavior of blood, in addition to the low capacity of water to uptake and release oxygen, in comparison with the role of hemoglobin in blood, intensify the inaccuracy of such a method. It has been basically suggested to use glycerol in order to alter the viscosity of a solution [5,21–24]. The mixture of water and glycerol was proposed, in 1993, by Kreulen et al. to be used in the experimental studies of hollow fiber membrane modules as gas–liquid contactors [24]. In 1994, Gourlay and Taylor used this solution for simulating blood oxygenation through CMOs in vitro [25]. Later on, Wickramasinghe et al. modified the non-Newtonian behavior of this mixture adding a small amount of xanthan gum, and investigated the gas exchange in CMOs using this solution as a blood analog fluid [5,23,26].

Various solutions have also been used as blood substitutes simulating its gas exchange performance. Mottaghy et al., in 1976, showed the possibility of using fluorocarbon in liquid oxygenators for the first time [27]. Some new studies proposed the application of hemoglobin-based artificial oxygen carriers as a substitute with natural blood [28]. In 2003, R.M. Winslow investigated different paradigms for the preparation and characterization of hemoglobin-based red cell substitutes [29]. In such approaches, oxygen can bind chemically to hemoglobin substitutes parallel to physically dissolving in water, which shows a comparable oxygenation affinity to natural blood. Therefore, these methods have a great advantage to the simple mixture of water and glycerol where there is no substitute for chemical binding with oxygen. However, these blood substitutes are rather expensive and not widely available; and therefore, the practical simulation of blood oxygenation through capillary membrane oxygenator remains challenging.

Sulfite solution is a novel alternative that demonstrates a high affinity for oxygen uptake [6]. It has been already used to investigate *OTR* in gas–liquid contactors as described by Hermann et al. [30]. Moreover, in a bioreactor where there is a living organism consuming oxygen, sulfite solution can be employed to simulate such metabolic procedures [21,22,30]. This method is based on the oxidation of sulfite ions while converting to sulfate ions in the presence of a metal catalyst (e.g. Fe^{+}, Cu^{+}, Co^{2+}, and Mn^{+}) [30].

The aim of the present study is to modify the sulfite solution, in regard with the oxygenation and rheological properties of natural blood, in order to simulate the *OTR* through CMOs precisely. The method is then validated by comparison of the results of in vitro investigations with native porcine blood in two types of commercially available CMOs.

Table 1
AAMI standard values for the inlet blood in in-vitro investigations of blood gas exchangers.

Parameter	Standard value	Std. dev.	Unit
S_{O_2}	65.0	±5.0	(%)
p_{O_2}	40.0	±5.0	(mm Hg)
p_{CO_2}	45.0	±5.0	(mm Hg)
C_{Hb}	12.0	±1.0	(g_{Hb}/dl_{blood})
BE	0.0	±5.0	($mmol_{base}/l_{blood}$)
T	37.0	±2.0	(°C)

2. Material and methods

2.1. Preparation of sulfite solution

The sulfite solution comprises sodium sulfite, Na_2SO_3 acts as an oxygen uptake component, phosphate buffer solution works as an inhibitor for sudden pH drop, and cobalt catalyst as an accelerator for oxygen uptake.

In order to prepare the buffer for the sulfite solution [21,22,30], 3.56 (g) of Na_2HPO_4 (Merck KGaA, Darmstadt, Germany) was added to 100 ml distilled and deionized H_2O and 3.12 (g) of NaH_2PO_4 (Merck KGaA, Darmstadt, Germany) in another 100 ml of distilled and deionized H_2O. To set the pH level 8, as an initial pH level, NaH_2PO_4 and Na_2HPO_4 should be mixed together with a ratio of 4.7 (ml) to 95.3 (ml) respectively. Because, the resulting phosphate buffer is 0.2 (M), 6 (ml) of this solution dilute to 100 (ml) using the distilled and deionized H_2O to reach the final molarity of 0.012. Afterwards, 90 (ml) of 0.012 (M) phosphate buffer was nitrogenized by direct inserting of nitrogen gas, to eliminate possible dissolved oxygen molecules in the solution.

For the purpose of achieving 100 (ml) of 0.5 (M) sulfite solution, as a reference solution, 6.302 (g) of Na_2SO_3 was added to the prepared nitrogenized buffer solution. Inserting sodium sulfite to the buffer solution causes some changes in the pH level; and therefore, the final solution's pH was adjusted at 8 by adding 30 wt. H_2SO_4 (Merck KGaA, Darmstadt, Germany) and distilled and deionized H_2O to reach 100 (ml) solution in the end [22].

As a catalyst substance, $CoSO_4$ (Merck KGaA, Darmstadt, Germany) was used in this study [30]. While the catalyst concentration has a direct effect on the reaction rate, a range of catalyst concentration was investigated by sets of experiments coming henceforth. The distilled and deionized water was provided using GFL double distillation water stills 2104 (GFL mbH, Burgwedel, Germany).

This viscosity of native porcine blood in the normal range of body temperature (37 (°C)) is about 3–4 (cP) [31]. In order to simulate the rheological properties of natural blood with the prepared sulfite solution, its viscosity should be altered toward that of natural blood. Usually, glycerol is used for changing the viscosity of an aqueous solution. However, we found that glycerol interferes with the oxidation reaction of sulfite solution due to its OH functional groups; and subsequently, pH does not change. Therefore, polyethylene oxide (PEO) (Sigma Aldrich, St. Louis, MO, USA) was employed in this study, as a substance without any interfering functional group, for changing the viscosity of sulfite solution.