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SCIENCE DIRECT®
Life Sciences 73 (2003) 2005–2018
Life Sciences
www.elsevier.com/locate/lifescie

Minireview

Utilization of in vivo ultrafiltration in biomedical research and clinical applications

Gea Leegsma-Vogt[a,*], Elsa Janle[b], Stephen R. Ash[c], Kor Venema[a], Jakob Korf[a]

[a] *Department of Psychiatry, Section Biological Psychiatry P7.26, University of Groningen, P.O. Box 30.001, 9700 RB Groningen, The Netherlands*
[b] *Purdue University, West Lafayette, IN, USA*
[c] *HemoCleanse, Inc., Lafayette, IN, USA*

Received 12 February 2003; accepted 15 April 2003

Abstract

Ultrafiltration (UF) is a filtrate selection method with a wide range of biomedical and clinical applications, including detoxification of blood in hemodialysis and peritoneal dialysis. New is, however, the use of UF as a convenient in vivo sampling method that, for example, has been used in diabetics. Ultrafiltration avoids complicated and time-consuming recovery calculations that are necessary when using in vivo microdialysis, as recoveries of low molecular weight molecules are near 100%. The subcutaneously or intravenously placed UF probes have been studied for off-line sample analysis and for continuous on-line monitoring, in a wide variety of species, including dogs, rats, pigs and humans.

This review discusses the potential of in vivo UF as a continuous tissue sampling technique in clinical research areas, and in several major biomedical applications including glucose and lactate monitoring and drug kinetic studies.

Keywords: Ultrafiltration; In vivo; Glucose; Lactate; Drug kinetics; Off-line; On-line

Introduction and scope

Ultrafiltration (UF) is used for the separation or purification of chemicals. UF has a wide variety of applications, from the mere separation of chemicals in the laboratory setting to the detoxification of

* Corresponding author. Tel.: +31-50-3612094; fax: +31-50-3611699.
E-mail address: g.vogt@acggn.azg.nl (G. Leegsma-Vogt).

0024-3205/03/$ - see front matter © 2003 Elsevier Inc. All rights reserved.
doi:10.1016/S0024-3205(03)00569-1

blood in hemodialysis and peritoneal dialysis in case of kidney failure (Hynes-Gay and Rankin, 2000; Ronco and Clark, 2001). New is, however, the use of in vivo UF as a convenient multiple sampling method.

In 1987 the first study was published on in vivo UF as a sampling technique alternative to microdialysis (Janle-Swain et al., 1987). Already in that article, its potential as a clinical device and a research tool was recognized. It was suggested that UF could be used in hospitalized patients in whom frequent biochemical parameters have to be monitored, without the necessity of repeated blood sampling (Janle-Swain et al., 1987). In the first pioneering studies, in vivo UF was used for sampling in awake, unrestrained animals such as dogs, but its use has been broadened since to rats, mice, rabbits, sheep, pigs, horses and humans. Thus far, most in vivo UF experiments are performed subcutaneously, but intravenous measurements and the ultrafiltration of saliva and bone have also been investigated. About 30 scientific papers on the use of in vivo UF as a sampling technique have appeared.

Recently another mini review on membrane sampling (microdialysis (MD) and ultrafiltration) from biological tissues appeared (Garrison et al., 2002), but that review mainly focussed on microdialysis in pharmacokinetics and pharmacodynamics. The present overview focuses upon the biomedical applications of in vivo UF and gives suggestions for clinical applications of UF, for example to monitor metabolism. First, we explain the principles of UF and outline the similarities and differences between MD and UF, discussing the advantages and disadvantages of UF as compared to MD. We will discuss the biomedical applications of in vivo UF on the basis of several UF studies, including subcutaneous and intravenous UF for monitoring glucose and lactate. Finally, combinations with analytical devices for off-line sampling and on-line analysis are proposed.

Principles of ultrafiltration

In vivo UF collects a filtrate of body fluids by applying negative pressure as a driving force. The molecular cut-off value of the semipermeable filtration membrane determines the maximum size of particles that can pass through the membrane. Also the configuration and charge of a molecule affects the membrane passing: for example, some small highly charged molecules such as gentamicin do not cross a polyacrylonitrile membrane. There are several materials that can be used as capillary semi-permeable membranes, for example regenerated cellulose, polycarbonate-ether, and polyacrylonitrile (Hsiao et al., 1990). Mostly membranes with a molecular cut-off value between 20 kD and 50 kD are used. By thus excluding larger particles like large proteins and cellular elements, the ultrafiltrated sample can be directly analyzed (Deterding et al., 1992; Paez and Hernandez, 1997).

The rate of fluid collection is determined by the amount of negative pressure applied, the membrane surface area and the hydraulic resistance, which is composed of the UF membrane type, the protein layers on the membrane surface, the surrounding tissue and the capillary walls near the UF probe. Membranes with high molecular weight cut-offs have lower resistance and thus allow higher flow rates. The flow-rate in subcutaneous UF probes ranges between 0.05 to 10 μl/min (0.07 to 14 ml/day), the outer surface area of current probes lies between 2 to 15 mm^2.

Frequent subcutaneous sampling of ultrafiltrate depends on the rapid replacement of interstitial fluid by the blood vessels. In tissue with limited blood flow rate and low replenishment of interstitial fluid only low sampling rates are possible. There are species differences in the applicability of UF, for example, the rat subcutaneous space allows better UF-sampling than human subcutaneous space