Computer models in bedside physiology
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Citation for published version (APA):

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Chapter 1
General Introduction; aims of the thesis

I have been trained in Biomedical Engineering (BME), a field that is, broadly speaking, geared to putting engineering methods to the assistance of clinical diagnosis and therapy. Biomedical engineering methods cover a wide range – from chemical engineering (tissue engineering and biomaterials) to electrical and mechanical engineering, as in the development of medical devices (12). In this thesis I apply bioelectrical (BME-) methods to solve several medical problems.

The thesis consists of two parts: the first part is about cardiovascular modeling and simulation; the second about analysis of beat-to-beat heart rate and blood pressure variability.

1. Modeling and simulation of the human cardiovascular system

Models of the circulation are constructed to help understand physiological problems or to simulate interventions which are difficult or impossible to perform in real life. In this thesis we have reduced a number of aspects of the human cardiovascular model to a computer program. A good model can accurately describe (some of) the behavior of a particular system; use of the computer model may reduce experiment time and cost, avoid unnecessary injuries and ethical controversies.

Since the first two-element Windkessel (arteries) model was developed in 1899 by Otto Frank (11), until the overall circulation regulation model developed in 1972 by A. C. Guyton(5), the cardiovascular models went from very simple to very complex. Today circulation models are developed simple or complex according to the research requirements. In the following two sections the medical background of our specific cardiovascular model is introduced. Modeling or simulation can never replace real experiments, but it can always make real experiments better, or smarter.

a. Cardiopulmonary Resuscitation simulation

Cardiopulmonary arrest (CPA, also called cardiac arrest, CA) is a condition in which the heart suddenly and unexpectedly stops beating. Data from the Sudden Cardiac Arrest Association (www.suddencardiacearrest.org) show that in the U.S.A more than 300,000 people suffer a CPA each year, only 8% of whom survive. When CPA occurs, cardiopulmonary resuscitation (CPR) is an emergency procedure to preserve brain function (and that of other vital organs) until further measures are taken to restore spontaneous circulation and breathing. No matter
Chapter 1

where CPA occurs: on the street or in a hospital, in-time and proper CPR and advanced life support can dramatically improve the survival rate to 50%! The International Liaison Committee on Resuscitation (www.ilcor.org) holds consensus meetings and publishes updated CPR guidelines every five years since the first in 2000. There are also free training courses (in hospitals, on websites, and in TV programs).

In Chapter 2 the question to be answered is: which CPR technique is the best one to improve cardiac output and organ perfusion? We compared five different CPR techniques, from conventional to innovative methods, by way of a cardiovascular circulation model.

In Chapter 3 the question to be answered is: if we apply all those efforts described in chapter 2 to improve cardiac output and organ perfusion, is that really the best we can do for the patient? When we pushed this CPR optimization we found that with high pressures of thorax and abdomen compression and large venous returns, we had to consider the lungs as well. With improved mechanical techniques, ‘faster and harder’ compressions are not difficult to obtain (in-hospital that is, with bare hands it is still difficult); the question is: can the lungs take it?

b. Pulse Pressure Variation simulation
Cardio-pulmonary interaction is in the spotlight again. Over the last 20 years pulse pressure variation (PPV) has proven itself as an accurate predictor of volume responsiveness (1, 2, 4, 7, 9, 10): lower PPV implies that the volume status has pushed cardiac filling to the plateau of the Frank-Starling curve to a saturation state(9). PPV is in clinical use to steer volume infusion for instance during surgery. However PPV does not work in situations like low tidal volume or spontaneous respiration(9). The question when PPV may reliably be used as indicator of volume responsive is still in discussion.

In Chapter 6 we use a cardiovascular circulation model, with respiration and ANS control to simulate how PPV changes with changes in circulating volume, whether PPV can predict volume responsiveness in different situations. We compare these results to recordings in healthy test subjects who received a large intravenous saline infusion.

2. Analysis of beat-to-beat heart rate and blood pressure variability
Before going into heart rate variability (HRV) and blood pressure variability (BPV), we have to talk about the autonomic nervous system (ANS) first. The autonomic nervous system is predominantly an efferent system transmitting impulses from the Central Nervous System (CNS) to peripheral organ systems. Its effects include control of heart rate and force of
contraction, constriction and dilatation of blood vessels, contraction and relaxation of smooth muscle in various organs, visual accommodation, pupillary size and secretions from exocrine and endocrine glands.

The ANS consists of two separate divisions: the parasympathetic and sympathetic systems, distinguished on the basis of anatomical and functional differences. The sympathetic nervous system aids in the control of most of the body's internal organs. Stress—as in the flight-or-fight response—is thought to counteract the parasympathetic system, which generally works to promote maintenance of the body at rest.

Disturbances of the autonomic nervous system can be the cause of serious health problems. Autonomic nervous system disorders can occur alone or as the result of another disease, such as Parkinson’s disease, alcoholism and diabetes. Therefore evaluation of the condition of the autonomic nervous system can be of diagnostic or predictive value.

a. **Heart rate variability (HRV) in CHF patients**
Heart rate variability (HRV) has emerged as a simple, noninvasive method to evaluate ANS activity. Reduced heart rate variability (HRV) is a powerful and independent predictor of an adverse prognosis in patients with heart disease and in the general population.

*In Chapter 4 we test which analysis method for HRV discriminates Chronic Heart Failure (CHF) patients on beta-blocker treatment from healthy control subjects; next we test which of these parameter(s) detects the situation where such a patient would ‘slip into’ a more sympathetic condition.*

b. **Challenge: Active standing up in Brugada patients**
When we stand up blood tends to shift towards the lower part of the body, sympathetic activity will raise heart rate, peripheral resistance, cardiac performance etc. to maintain blood pressure, at the same time parasympathetic activity will withdraw.

Active standing-up from supine or sitting is clinically used to test ANS function in control of blood pressure and heart rate (3, 6, 8, 13).

*In Chapter 5 we compare the change of beat-to-beat parameters like heart rate, blood pressure from supine to upright position in healthy control subjects and Brugada patients. The Brugada syndrome (BrS) is a genetic disease that is characterized by abnormal ECG-findings and an increased risk of sudden cardiac death. The stand test is used to test the*
function of the ANS in Brugada patients and, ultimately, to find predictors for the risk of sudden cardiac death.

3. Chapter overview

In all there are seven chapters, as follows:

1. General introduction and aims of the thesis;
2. Optimal cardiopulmonary resuscitation as tested by computer modeling;
3. Abdominal counter pressure in CPR: What about the lungs? An in silico study;
4. Search for HRV-parameters that detect a sympathetic shift in heart failure patients on β-blocker treatment
5. A subgroup of Brugada patients shows low orthostatic blood pressures as a sign of decreased sympathetic outflow
6. Dynamics of pulse pressure variability and the difficulty of predicting fluid responsiveness;
7. Summary and general conclusions

See the flowchart in Figure 1.

References


