THE RAPID RESPONSE SYSTEM

EFFECTS OF EARLY IDENTIFICATION AND TREATMENT OF PHYSIOLOGICAL INSTABILITY

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To my family, with love
ABSTRACT

Adverse events occur to hospital patients, with potentially fatal consequences. Unfortunately, preceding warning signs are not always recognized and acted upon correctly. There exists a mismatch between patients’ needs and the resources available in general wards. Hospital structures need to be developed to provide systematic approaches to find and treat deteriorating ward patients before their condition becomes irreversible. The Rapid Response System (RRS) is one such approach, a complex interventional framework that extends critical care to patients with sudden deterioration, wherever they are located in the hospital.

A team dedicated to this process, the Rapid Response Team (RRT), or in Swedish: Mobil Intensivvårds Grupp (MIG) was introduced at the Karolinska University Hospital Solna in March 2005. The team is composed of a physician and nurse from both the intensive care unit and the ward. Together they convene bedside when a patient fulfills predefined physiological criteria based on easily measured vital signs. The system provides hospital staff with the tools to recognize early signs of clinical deterioration and prompt access to critical care expertise in an effort to improve the process of care and overall safety for hospital patients.

The aim of this thesis was to evaluate the effects that the RRT has had at Karolinska on several levels: the reduction of cardiac arrests and hospital mortality, the detection of patients in need of a higher level of care and the role that the RRT plays in ethical decisions on patient care.

The implementation of the RRT was associated with a decrease in both cardiac arrests and overall adjusted hospital mortality. The patients who appeared to benefit most from the system were medical patients and surgical patients that did not undergo surgery. The RRT was able to detect vulnerable patients, predominantly those of older age with multiple co-morbidities who are at high risk of unrecognized events. We explored the concept of the deteriorating ward patients also in another setting and found that the problem is of similar characteristics and magnitude in Sweden as well as in Australia. The majority of patients examined by the RRT could continue treatment in general wards but around ¼ of the patients were in need of a higher level of care. We examined the two modes of admission into intensive care from general wards and describe that the RRT detected complex patients at the wards to a greater extent than did the traditional triage system. Severe sepsis was the condition most often identified by the RRT, a condition that benefits greatly from early detection. Finally, we found that the RRT is frequently involved in discussions and decisions concerning end-of-life care.

Key words: rapid response system, rapid response team, medical emergency team, cardiac arrest, mortality, limitation of medical treatment
LIST OF PUBLICATIONS

This thesis is based on the following papers, which will be referred to by their Roman numerals as indicated below:

I. Reducing in-hospital cardiac arrests and hospital mortality by introducing a medical emergency team
   Konrad D, Jäderling G, Bell M, Granath F, Ekbom A, Martling C-R
   *Intensive Care Medicine* 2010, 36(1):100-106

II. The deteriorating ward patient: a Swedish-Australian comparison
    Jäderling G, Calzavacca P, Bell M, Martling C-R, Jones D, Bellomo R, Konrad D

III. ICU admittance by a Rapid Response Team versus conventional admittance, characteristics and outcome
    Jäderling G, Bell M, Martling C-R, Ekbom A, Bottai M, Konrad D
    *Critical Care Medicine* 2013, 41(3):725-31

IV. Limitations of medical treatment and long-term outcome in patients attended by the Rapid Response Team
   Jäderling G, Bell M, Martling C-R, Ekbom A, Konrad D
   Submitted manuscript
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<td>Karolinska</td>
<td>Karolinska University Hospital Solna</td>
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<tr>
<td>RRS</td>
<td>Rapid Response System</td>
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<td>Rapid Response Team</td>
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<td>Medical Emergency Team</td>
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<td>MIG</td>
<td>Mobil Intensivvård Grupp</td>
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<td>MEWS</td>
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<td>NEWS</td>
<td>National Early Warning Score</td>
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<td>High Dependency Unit</td>
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<td>CA</td>
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<td>Length of Stay</td>
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<td>PIN</td>
<td>Personal Identity Number</td>
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<td>IPR</td>
<td>Inpatient Register</td>
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<tr>
<td>NBHW</td>
<td>National Board of Health and Welfare</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<td>OR</td>
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<td>RR</td>
<td>Relative Risk</td>
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<td>SE</td>
<td>Standard Error</td>
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INTRODUCTION

The evolution of healthcare has been rapid over the last century. Hospital structures and the demographics of our population in general are changing. We are faced with the task of providing more care to sicker and older people. Technological development progresses, we have sophisticated apparatus to use and diagnostic tools to guide us. At the same time, something is lost on the way as principles of measuring and even more importantly, understanding basic vital signs are neglected. Complex patients in general wards stand at risk of unrecognized deterioration which can lead to fatal consequences, something that holds little acceptance with today's enlightened patient population. There is plenty of evidence that serious adverse events occur to hospital patients and that the majority may be preventable (1-4).

Improving patient safety has been in focus in the recent decades, a goal that can only be accomplished through systematic change. One organized approach is the Rapid Response System (RRS), an effort to bring intensive care knowledge outside the walls of the unit. It bridges across specialties and hierarchies and aims to center care on the deteriorating patient before irreversible harm occurs. The implementation of an RRS is an evolution that reinforces the importance of paying attention to basic vital signs and a system that empowers the staff with direct access to critical care expertise. It may sound simple but is in fact a complex intervention, acting on many levels in the hospital structure.

Rapid Response Systems have been widely adopted in different forms and although the concept holds strong face value, it needs to be assessed as any other intervention. The four papers included in this thesis describe the impact of the RRS at Karolinska University Hospital Solna, since its introduction in year 2005. In study I, we examine the frequency of cardiac arrests as well as overall adjusted hospital mortality two years following the implementation of the RRS. Study II is a comparison of the characteristics and outcome of deteriorating ward patients at Karolinska in Sweden and at Austin Hospital in Melbourne, Australia. Study III evaluates the intensive care unit outcome for the RRS patients and compares it with the outcome of patients admitted to intensive care through the conventional triage system in general wards. Study IV examines the role of the RRS when making ethical decisions about setting limits to medical interventions.
BACKGROUND

HISTORICAL SETTING

The history of hospitals

The concept of dedicated places for healing the sick has been described to date back to as early as ancient Mesopotamia and the Buddhist monasteries of Hindustan in 900 BC (5). The Greek provided care at temples in the 4th century BC, as in the temple of Asclepius and the Romans developed military hospitals across their empire. As Christianity spread, so did the Church’s influence in caring for the sick and religion continued to dominate the establishment of hospitals well into the 16th century. Monasteries had pharmacies and gardens with medicinal plants but were equally concerned with attending to the well-being of the soul as the body. Wards were configured with rooms radiating out from the altar in the center so as to provide recovery or solace for all patients easily. In a similar design, wards later became centered around the nursing station so that instead nurses could assist with recovery. In the 18th century, hospitals were becoming horrific places. As the wards became larger, they also became more dangerous. Sanitation was inexistent, cross-infection common and mortality high, leading to the conception among the public of hospitals being “gateways to death” (6). It took until the beginning of the 20th century to amend this view.

The history of Karolinska

The first teaching hospital that also provided acute health care in Stockholm was opened in 1752, Kongl. Seraphimerordenslazarettet (7). Initially providing 8 beds, 4 for women and 4 for men, it grew to just over 500 beds by the beginning of the 1900s. It was realized that a new teaching hospital was necessary to house the increasing health care needs of the growing population and for education of medical staff and research. The plan to build a new university clinic in close proximity to Karolinska Institutet was approved in 1931 and in 1940 the Karolinska Hospital opened in Solna with 1 058 beds, staffed on the opening day by 74 doctors, 22 nurses and 164 cleaning ladies (7).

In 1972 another university hospital, Huddinge Hospital was opened in Stockholm. The organizational merger of Karolinska and Huddinge on January 1st 2004 resulted in Karolinska University Hospital, one of the largest teaching clinics in Europe. Today it holds a total of 15 500 employees and 1 700 beds at all sites. Karolinska Solna is the trauma referral center of the entire Stockholm area and the only site that holds cardiothoracic and neurosurgical units. The hospital building has however aged considerably and is impractically spread out over a large area and many separate buildings. Therefore an entirely new hospital is under construction on the original grounds: New Karolinska Solna, expected to open in 2016.
The history of intensive care

Florence Nightingale could be claimed to have been the first to introduce the concept of critical care. In her service during the Crimean war in the mid-1850s she did this by moving the sickest patients on her ward closest to her station where she could keep a constant watch over them and provide instant care, if needed (8). However, we count the dawn of intensive care to when Bjørn Ibsen in Copenhagen applied the widespread use of tracheostomy and positive pressure ventilation, for hundreds of patients, manually by hundreds of medical students, for hundreds and thousands of hours in the polio epidemic of the 1950s, dropping mortality rates drastically. This was the beginning of critical care, with anesthesiologists for the first time stepping out of the operating rooms and into these new units, specialized in providing for the sickest patients, that we now know as intensive care units (9,10).

SYSTEM FAILURE

It may seem a strange principle to enunciate as the very first requirement in a hospital that it should do the sick no harm
- Florence Nightingale

The expansion of medical knowledge since Ibsen’s days and the advances in surgical techniques, drug treatments and interventions make it possible to treat conditions which would not have been possible to treat only 50 years ago. This provides both physicians and patients with sometimes unrealistic expectations. Hospitals in the western world today are generally considered to be well controlled environments, trusted by patients to provide high standard of care, professionalism and correct management of their illnesses.

All may not be so well, however. Progress has also led to a change in demographics, with a yet unparalleled rising age curve and as a result, an increasing level of illness.

![Figure 1. Temporal trend of the number of people aged 65 or more in the county of Stockholm, 1968-2011. From Statistiska centralbyrån (SCB).](image)
Background

This is coinciding with some unfortunate trends in hospital care. Health care budget containments, cuts in the number of beds available, shortage of trained nurses and working time directives do not match the rising demand for admissions, with fewer and less experienced staff at hand to manage a larger workload of more complex patients (11). The intensive care unit (ICU) can only provide proportionately few number of beds and the gap over to general wards when it comes to monitoring, vigilance and staffing level is simply enormous (10).

Advancement in medical technology has also led to the development of specialization and expertise in narrow fields. Although inevitable and necessary, this has not been without drawbacks. Experts tend to lose the knowledge and experience of overall care for patients with acute deterioration that deviate from the expected. Specialized wards and specialized professionals are trained to handle the diseases of single organs well but are less skilled in managing a complex patient that becomes seriously ill outside the box.

Adverse events

In a study of more than 30 000 discharges from 51 hospitals in New York State in 1984 it was concluded that adverse events occurred in 3.7% of hospitalizations and that 58% of these could have been prevented. An adverse event was defined as an injury caused by medical management rather than the underlying condition of the patient and a preventable adverse event as an adverse event attributable to error. Although most events led to disability lasting less than six months, 13.6% led to death and 2.6% to permanent disabling injury (1). Following this and other studies (4,12-14) the Institute of Medicine published a landmark report “To Err is Human” in 1999, revealing a significant problem with patients’ safety in the United States. It was extrapolated that as many as 98 000 Americans die in hospitals each year as a result of preventable medical errors (15), or the equivalent of one Boeing jet crashing every day of the year. Similar reports emerged from other countries as well (3,16-19), and a call to action started taking form (20) with a shift towards concentrating on safety in hospitals.

Antecedents

Once it was recognized that adverse events do occur, it soon followed that most events were in fact preceded by warning signs (21). Through review of records, it became clear that in 84% of cardiac arrests there were documented physiological abnormalities in variables such as heart rate, respiratory rate and mental status, up to 8 hours before the arrest (22). This slow deterioration of vital signs, even up to 48 hours before serious adverse events such as cardiac arrests, unanticipated ICU admission or hospital death has been confirmed in several other studies (21,23-27).

So it stands that the development of critical illness is not so much sudden as suddenly recognized (28).

In-hospital cardiac arrests occurring in general wards are mostly related to non-cardiac processes, with the “cardiac arrest” representing the common final pathway of a variety
of underlying disturbances (22). Hence, it is not surprising that over the past 30 years, mortality rates after in-hospital cardiac arrests have remained high, not dropping below 85-90% (29-33).

When examining patients admitted to intensive care, ward patients were identified as especially vulnerable. If admitted from a general ward, mortality rate was twice as high as for patients admitted from the operating/recovery room or emergency room (34) and the longer they had stayed in hospital before ICU admission the higher the risk of mortality, even after case-adjustment (35). Confidential inquiries into the quality of care before ICU admission by blinded investigators concluded that as many as 54% of patients had received suboptimal care in the wards, resulting in a worse outcome (36,37).

**RAPID RESPONSE SYSTEMS**

*Better three hours too soon than a minute too late*

- William Shakespeare

The above mentioned realizations that there were patients at risk of faring ill within hospitals were the basis for evolving systematic solutions to improve patient safety. One approach emanated from the intensive care units: dedicated teams that could be summoned to respond to deteriorating patients, foregoing the usual boundaries of specialties and locations, centering instead around the patients’ needs.

**The history of Rapid Response Systems**

Systems were being formed in the beginning of the 1990s, in Pittsburgh under the denotation “Condition C” (crisis) as opposed to “Condition A” (arrest), and in Australia as the Medical Emergency Team (MET). The first description in the literature appears from an Australian center in 1995 (38), describing the utilization of the team, its triggers and interventions. In the United Kingdom, a similar model was named the “Patient-at-risk Team” (39).

In 2005, the first international conference on Medical Emergency Teams was held in Pittsburgh and the faculty consensus findings published (40), defining the needs for and composition of Rapid Response Systems (RRS) as well as evaluating the data available and setting recommendations for future outcome measurements.

**Components of the RRS**

The term Rapid Response System refers to an entire system for responding to patients with a critical medical problem (28). Hospitals have adopted different names or compositions based on local preferences, like the Medical Emergency Team, Rapid Response Team (RRT), Critical Care Outreach Team, or as in Sweden: *Mobil Intensivvårds Grupp (MIG)*. Teams may be led by physicians, such as in the METs or nurse led as in outreach teams. In our studies and in this thesis, we use the terms RRT
and MET synonymously, denoting a team led by a physician from the intensive care unit.

The system can further be divided into the afferent limb which consists of the detection and trigger that the patient is deteriorating and the efferent limb which is the response itself by the team. Two additional elements have been described that are useful in implementing, upholding and improving the program: an administrative structure and an evaluative process for feedback and quality control (28).

Figure 2. The components of a Rapid Response System. Reproduced from the Textbook of Rapid Response Systems (28), with kind permission from Springer Science+Business Media.

The afferent limb deserves some mention because it probably is the most critical component. Without detection there can be no response and then it will be irrelevant which form of team one has. The afferent limb is a chain of events and as such, prone to errors at several steps. A deterioration must first be followed by observation, then recognition that something is wrong, leading to a decision to call for help, knowing who to call, actually making the call which in turn must be received, and first then can a response be elicited.

**Trigger criteria**

*If you don’t take a temperature, you can’t find a fever*

- Law #10 of the House of God

The classic vital signs are temperature, pulse rate, blood pressure and respiratory rate (28). Oxygen saturation as measured by pulse oximetry and level of consciousness have also been proposed as useful vital signs (41-43). Derangements of these physiological markers make up the triggers that activate the RRT response. Different “track and trigger” systems exist and can be categorized as single-parameter, multiple-parameter,
aggregate weighted scoring or combination systems (28), of which the two most common are the single parameter and the aggregate weighted score systems. Variables included are empirically based on clinical experience and may vary slightly across centers. In the United Kingdom, there is a predominance of the aggregate weighted scoring system where deviations of vital signs are assigned different points and summed up to a total score, known as the Early Warning Score or Modified Early Warning Score (MEWS) (44). The advantage is that a trend of the score can be followed over time and be used to direct a graded escalation of care but the drawback is that it is relatively complex, can be time-consuming and possibly inaccurately calculated (45). There exist several local adaptations of the scoring system, where for example some include urinary output and some do not. In the United Kingdom a national standard has recently been proposed by the Royal College of Physicians, known as the National Early Warning Score (NEWS) (46).

**National Early Warning Score (NEWS)**

<table>
<thead>
<tr>
<th>PHYSIOLOGICAL PARAMETERS</th>
<th>3</th>
<th>2</th>
<th>1</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiration Rate</td>
<td>≤6</td>
<td>9 - 11</td>
<td>12 - 20</td>
<td>21 - 24</td>
<td>≥25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxygen Saturations</td>
<td>≤91</td>
<td>92 - 93</td>
<td>94 - 95</td>
<td>≥96</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any Supplemental Oxygen</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature</td>
<td>≤35.0</td>
<td>35.1 - 36.0</td>
<td>36.1 - 38.0</td>
<td>38.1 - 39.0</td>
<td>≥39.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td>≤90</td>
<td>91 - 100</td>
<td>101 - 110</td>
<td>111 - 219</td>
<td>≥220</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart Rate</td>
<td>≤40</td>
<td>41 - 50</td>
<td>51 - 90</td>
<td>91 - 110</td>
<td>111 - 130</td>
<td>≥131</td>
<td></td>
</tr>
<tr>
<td>Level of Consciousness</td>
<td>A</td>
<td>V, P, or U</td>
<td></td>
<td></td>
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</table>

Figure 3. National Early Warning Score (NEWS), from the Royal College of Physicians (46).

In the first description of a MET system (38), the triggers consisted of specific conditions, physiological abnormalities and the non-specific criterion “any time urgent help is needed” of which any one was sufficient to call the team. These original MET calling criteria are, with slight modifications, still in use in Australia and the US. Compared to aggregate scores, the single parameter system is simple to implement, easy to use and provides an all-or-nothing response (call for help or not). The criteria consist of the observation of an acute change in either: respiratory rate, pulse oximetry saturation, heart rate, systolic blood pressure, conscious state or that the staff is simply worried about the patient.

The “worried” criterion is important and empowers staff to call the team on the sole reason that they are concerned about a patient. It relies on the intuition and experience
Background

of nurses and should not be underestimated, as subtle symptoms or small changes picked up on by vigilant nurses often turn out to be precursors to more objective physiological changes (47).

In Sweden, both systems can be found. The best method for recognizing a potential problem with a patient and triggering a response is still unknown, and systems are generally prone to low sensitivity and positive predictive values but high specificity and negative predictive values. The low sensitivity can be improved by reducing the trigger threshold but not without compromising specificity, thus increasing workload (48).

THE RAPID RESPONSE SYSTEM AT KAROLINSKA

The Rapid Response System was introduced at Karolinska Solna in March 2005, following thorough preparations, the forming of an administrative group and a three month long educational period.

Based on the experiences from Australia, the single parameter scoring system was chosen at Karolinska, adapted from Bellomo et al (49). Before the implementation of the team however, a prevalence study was undertaken to assess the adequacy of the criteria locally and also to get an estimate of the possible workload (50). All in-hospital patients were screened for physiological data and followed for mortality. Of all the patients examined, 4.5% were found to have deviating vital signs. Fulfilling any of the criteria at a single time led to an almost 10-fold increase in mortality at 30 days as compared to patients not fulfilling criteria.

![Kaplan-Meier curve of survival by patient category.](image)

Figure 5. Kaplan-Meier curve of survival by patient category. Study criteria +: patients that fulfilled any of the physiological trigger criteria; study criteria -: no criteria fulfilled. Not present, not possible or no consent: patients not examined. From Bell et al (50), reproduced with permission.
Extending the limits of the criteria was found to increase workload beyond benefit but restricting the criteria, on the other hand, led to missed mortalities. On the basis of this study, the criteria were found valid and chosen for use at Karolinska. The team is to be called if there is an acute change in vital parameters to any of the following: respiratory rate <8 or >30/minute, pulse oximetry saturation <90% despite oxygen administration, systolic blood pressure <90 mm Hg, heart rate <40 or >130/minute, sudden change in conscious state or if staff member is worried about the patient.

Figure 4. The RRT criteria, as used at Karolinska University Hospital Solna.

Implementation

During a three-month educational period, all members of staff at the wards were informed on at least two occasions of the objectives and functions of the RRT. Clinic meetings were held for informing physicians of all specialties at least once. The only wards not included were the pediatric and cardiothoracic as they are geographically separated from the main building and serviced by their own independent intensive care units. Information was made available on the hospital intra-net and posters were displayed in all wards, encouraging any member of the staff to make the call. Pocket-size cards with the criteria and phone number to the team were printed and distributed to all staff. Contact persons at each ward were appointed to facilitate continued education and feedback loops after implementation. The RRT was then launched covering all wards 24 hours a day, 7 days a week.
Team composition

The Rapid Response Team at Karolinska consists of a physician and a nurse from the general ICU and the physician and nurse responsible for the patient at the ward. The team meets bedside around the patient and after a joint assessment an individual plan is made. This may include new treatment, directives for further evaluations, decision to transfer to a higher level of care or discussing limitations of medical treatment. The joined effort of forces from both the ICU and the staff from the ward is important because each bring their own expertise, the ICU staff contributing critical care experience and the ward staff their background knowledge of the individual patient and details of what has led to the present condition.

A cardiac arrest team has been in use at the hospital since the early 1990s, responding to codes where there is no palpable pulse, no measurable blood pressure, unconsciousness and the need for immediate cardiopulmonary resuscitation. The code goes out to an anesthesia resident, ICU nurse and internal medicine specialist through the switchboard. The average time from page to arrival of team on scene is 2.5 minutes. The cardiac arrest team has been left unaffected and separate from the RRT, with great emphasis placed on keeping the two situations apart. The RRT is more of a rapid second opinion and has no predefined time for appearance although it will be as prompt as possible. The ICU physician who answers the RRT phone has to make a priority of the urgency of the call against other obligations presently at the ICU. Despite this, there is seldom a long delay and the average time from call until the team convenes bedside is 13.2 minutes.

In conclusion, the goal of the system is to improve the quality of care and safety for in-hospital patients and reduce their risk of adverse events, such as cardiac arrest and unexpected death. We hope to do this through the continuous education of staff of the importance of failing vital signs, identifying patients at risk earlier and providing a rapid and adequate response.
AIMS OF THE STUDY

We evaluated several aspects of the Rapid Response Team at Karolinska University Hospital Solna. Our specific aims were:

1. To investigate the effect of introducing an RRT on in-hospital serious adverse events, such as cardiac arrest rate and overall hospital mortality.

2. To compare the demographics and outcome of our cohort of RRT patients with another center in a different country, aiming to investigate generalizability of the Rapid Response System.

3. To examine the two modes for patients to be admitted into intensive care from general wards: through an RRT call or through conventional contact, with the aim to evaluate and compare admitting diagnoses, severity scores on admission, length of stay and mortality.

4. To investigate the role of the RRT in the issuing of limitations of medical treatment and to describe the characteristics and outcome of these patients.
MATERIAL AND METHODS

REGISTERS AND DATABASES

The Swedish National Registration Number

All Swedish residents are at birth, or permanent immigration, assigned a unique ten-digit personal identity number (PIN) by the National Tax Board (51). This number is widely used for administrative purposes such as population statistics, passports and identification, taxation, social security etc., but also in health care as the unique identifier in medical records. The PIN also enables individual linkages between different registers (52).

The Swedish Inpatient Register

The Swedish National Inpatient Register (IPR), also called the Hospital Discharge Register, is a main source of data for register-based research. The IPR was launched by the Swedish National Board of Health and Welfare (NBHW) in 1964 and holds complete nationwide coverage since 1987. Together with the unique PIN, each record contains diagnoses at discharge, coded according to the International Classification of Diseases-7 (ICD-7) during 1964-1967, ICD-8 during 1968-1986, ICD-9 during 1987-1996, and ICD-10 thereafter. It also contains the following variables: sex, age at discharge, hospital, type of department, date of admission and discharge, duration of admission, elective or acute healthcare, mode of admission and discharge, and codes for surgical procedures. The validity of the IPR is regarded as high with 85-95% of diagnoses shown to be correct (53).

The Cause of Death Register

The Cause of Death Register is managed by the NBHW and contains dates and causes of death for all deceased Swedish residents. The causes of death are coded according to ICD-10 with underlying cause of death and up to 20 multiple causes. Persons without PIN (stillborn infants, persons seeking asylum or temporary visitors) are not included. The register is updated yearly and coverage is estimated to exceed 99% (54).

The Rapid Response Team database at Karolinska

The Rapid Response Team (in Swedish: MIG, Mobil Intensivvårds Grupp) at Karolinska University Hospital in Solna was initiated on the 7th of March 2005. Calls to the RRT are documented in a separate database as well as a note made in the patient’s medical record. Variables collected are patient related, call related and administrative. When needed, information was complemented from medical records. This database was used for all studies.
The Patient Database Management System in the ICU

All patients admitted to the general ICU at Karolinska Solna are connected to the Patient Database Management System (Clinisoft®, GE Healthcare). The system stores information on admission and discharge times, diagnosis codes, physiological variables, severity scoring (APACHE II), procedures and limitation of medical treatment. Information from this database was used in study III.

STUDY POPULATIONS AND DATA COLLECTION

Table 1. Overview of the subjects and methods used in the thesis

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Population</th>
<th>Number of subjects</th>
<th>Follow-up</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Single center before and after cohort study</td>
<td>All patients admitted to Karolinska 2000-2006</td>
<td>277,717</td>
<td>180 days</td>
<td>Cardiac arrest rate and mortality</td>
</tr>
<tr>
<td>II</td>
<td>Two centers, international observational cohort study</td>
<td>RRT patients at Karolinska and Austin aug 2005-aug 2007</td>
<td>2,207</td>
<td>30 days</td>
<td>Mortality</td>
</tr>
<tr>
<td>III</td>
<td>Single center observational cohort study</td>
<td>Patients admitted to Karolinska general ICU from the wards 2007-2009</td>
<td>643</td>
<td>1 year</td>
<td>Mortality</td>
</tr>
<tr>
<td>IV</td>
<td>Single center observational cohort study</td>
<td>All RRT patients at Karolinska 2005-2010</td>
<td>1,818</td>
<td>180 days</td>
<td>Limitation of medical treatment and mortality</td>
</tr>
</tbody>
</table>

Study I

All patients admitted to the Karolinska University Hospital in Solna from January 1st 2000 to December 31st 2006 were included in the analysis. Incidence of in-hospital cardiac arrest (CA) was recorded and hospital length of stay (LOS), mortality and patient co-morbidities were assessed using the Inpatient Register. The control period ran from 2000 to 2004 and the intervention period from 2005 to 2006. The educational period preceding RRT implementation was included in the intervention period as the increased awareness due to intense educational efforts might in itself have an effect on
the outcome measures. Characteristics of RRT calls were gathered from the RRT database.

**Study II**

815 RRT calls for 640 patients at Karolinska University Hospital Solna were compared with 2 248 RRT calls for 1 567 patients at Austin Hospital in Melbourne, Australia. The study period ran from August 15th 2005 to August 15th 2007. Data collected included patient characteristics, reasons for RRT activation, timing of RRT activation, and patient outcome following the call.

**Study III**

During the study period between 2007 and 2009 there were 2 571 admissions to the general ICU at Karolinska University Hospital Solna. Of these, 694 were admitted from the general wards and included in the study. Excluded were 796 trauma admissions, 539 from the emergency room, 293 from the operating/recovery room, 115 from other hospitals, 34 from other wards in the hospital not covered by the RRT and 10 due to missing data. Patients included were classified based on whether they had been admitted to the ICU by the RRT or not. Information was collected from the patient database management system in the ICU, such as admission diagnosis, severity scoring (APACHE II), date and time for admission and discharge, procedures and if applicable, limitation of medical treatment. Co-morbidities and mortality was retrieved from the Inpatient register and the Cause of Death register.

**Study IV**

All RRT calls from March 2005 to December 2010 were included. During the study period there were 2 241 RRT activations. 35 were excluded due to missing data, 1 was excluded for being < 16 years old and 16 were excluded as they were not admitted to the hospital (daycare patients or visitors). Therefore, 2 189 RRT calls in 1 818 unique hospital admissions were included. Information analyzed was the circumstances regarding the RRT call and patient characteristics including limitations of medical treatment and mortality. The RRT database was used together with the Inpatient and the Cause of Death register. We also examined the frequency of in-hospital cardiac arrests during the study period.

**STATISTICAL ANALYSIS**

Crude comparisons of proportions were assessed by chi-square test or Fischer’s exact test for categorical variables. Continuous variables were compared using non-parametric test (Mann-Whitney U test) and reported as medians with interquartile ranges (IQR). *P*-values < 0.05 were considered significant.

In Study I, hospital mortality before and after RRT implementation was compared using conditional logistic regression, conditioned on age in 5 year groups, sex, length of
stay, type of admission, acute or elective admission and co-morbidities. Results were presented as Odds ratios (OR) with 95% confidence intervals. In Study III, logistic regression was used with mortality at 30 days and 1 year respectively as the dependent variable to assess the independent effects of age, sex, length of stay, predefined co-morbidities, type of hospital admission (medical/surgical and acute/elective) and limitation of medical treatment. Results were presented as Odds ratios (OR) with 95% confidence intervals and p-values assessed by Wald’s test.
RESULTS

However beautiful the strategy, you should occasionally look at the results
- Winston Churchill

STUDY I

The aim of this study was to assess cardiac arrest rate and overall hospital mortality in a period two years following RRT implementation as compared to a five year control period before.

Baseline characteristics of all patients admitted to Karolinska before and after RRT implementation are shown in Table 2. During the RRT period the number of admissions/year was lower, patients were slightly younger and more frequently electively admitted. These patients however carried significantly more co-morbidities in the form of malignancies, chronic obstructive pulmonary disease and renal failure.

Table 2. Characteristics of patients admitted to the Karolinska University Hospital Solna during the study period

<table>
<thead>
<tr>
<th></th>
<th>Pre-MET</th>
<th>MET</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admissions/year (range)</td>
<td>40778 (37671-43663)</td>
<td>36913 (36272-37553)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medical admissions (%)</td>
<td>40.5</td>
<td>35.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SURG-OP admissions (%)</td>
<td>45.4</td>
<td>53.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SURG-nonOP admissions (%)</td>
<td>14.2</td>
<td>11.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Acute / Elective</td>
<td>67.4/32.6</td>
<td>62.6/37.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female/Male</td>
<td>60.1/39.9</td>
<td>60.4/39.6</td>
<td>NS</td>
</tr>
<tr>
<td>Age (years, SD)</td>
<td>53.1 (21.1)</td>
<td>52.4 (20.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospital LOS (days, SD)</td>
<td>4.4 (6.8)</td>
<td>4.3 (6.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>5.6</td>
<td>5.6</td>
<td>NS</td>
</tr>
<tr>
<td>Renal failure (%)</td>
<td>2.4</td>
<td>2.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ischemic heart disease (%)</td>
<td>3.8</td>
<td>3.8</td>
<td>NS</td>
</tr>
<tr>
<td>Heart failure (%)</td>
<td>4.1</td>
<td>3.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>COPD (%)</td>
<td>1.8</td>
<td>2.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Malignancy (%)</td>
<td>28.2</td>
<td>30.0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Crude hospital mortality was lower in the period following RRT implementation, 1.64% vs. 1.89% before. Potential confounding factors were the shifts of patient characteristics in the two periods. Adjustment for this in the regression model yielded an OR for hospital mortality of 0.90 (95% CI 0.84-0.97) overall (Table 3). Results were different for medical and surgical patients. Medical patients showed an adjusted OR of 0.88 (95% CI 0.81-0.96), patients admitted for surgical reasons but not operated upon had the greatest reduction in mortality with an adjusted OR of 0.72 (95% CI 0.56-0.92) while surgical patients that were operated did not seem to benefit.

Table 3. Hospital mortality before and after RRT implementation compared by conditional logistic regression

<table>
<thead>
<tr>
<th></th>
<th>Hospital mortality (%)</th>
<th>p-value</th>
<th>Model 1, adjusted Odds Ratio (CI), p-values</th>
<th>Model 1, adjusted Odds Ratio (CI), p-values</th>
<th>Model 2, adjusted Odds Ratio (CI), p-values</th>
<th>Model 2, adjusted Odds Ratio (CI), p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-MET</td>
<td>MET</td>
<td>MET vs. Pre-MET</td>
<td>MET vs. Pre-MET</td>
<td>MET vs. Pre-MET</td>
<td>MET vs. Pre-MET</td>
</tr>
<tr>
<td>Total</td>
<td>1.89</td>
<td>1.64</td>
<td>&lt;0.001</td>
<td>0.94 (0.88-1.01)</td>
<td>0.08</td>
<td>0.90 (0.84-0.97)</td>
</tr>
<tr>
<td>MED</td>
<td>3.24</td>
<td>3.09</td>
<td>0.24</td>
<td>0.93 (0.86-1.01)</td>
<td>0.09</td>
<td>0.88 (0.81-0.96)</td>
</tr>
<tr>
<td>SURG-OP</td>
<td>0.81</td>
<td>0.81</td>
<td>0.95</td>
<td>1.07 (0.93-1.23)</td>
<td>0.36</td>
<td>1.09 (0.95-1.26)</td>
</tr>
<tr>
<td>SURG-nonOP</td>
<td>1.45</td>
<td>1.12</td>
<td>0.02</td>
<td>0.73 (0.57-0.93)</td>
<td>0.01</td>
<td>0.72 (0.56-0.92)</td>
</tr>
</tbody>
</table>

Model 1: adjustments for age, sex, hospital length of stay and type of admission (elective or acute, medical or surgical).
Model 2: additional adjustments for co-morbidities (diabetes, renal failure, chronic obstructive pulmonary disease and malignancy).
Results

Cardiac arrest rate was low to begin with, 1.12/1000 admissions over the five years preceding implementation and was still significantly reduced to 0.83/1000 admissions in the RRT period, a reduction of 26%.

![Cardiac arrests/1000 adm.](image)

Figure 6. Cardiac arrests/1000 admissions in the years 2000-2006.

**STUDY II**

Characteristics and outcome of RRT patients in two different centers, Karolinska in Sweden and Austin in Australia were compared and found to be similar. Although Austin had a higher proportion of RRT calls, the type of patients in need of RRT attention was the same. There were slightly more activations for medical vs. surgical patients at both centers (50.9% at Karolinska vs. 51.1% at Austin), patients were predominantly of older age (mean age 66.5 vs. 69.4 years) and most RRT calls were made after office hours (56.7% vs. 55.8%). The majority of RRT patients at both sites had been in hospital > 3 days before the call, 53.9% vs. 54.9% and the proportion of multiple calls was 19.5% at Karolinska and 22.8% at Austin. At both centers the most common reason for calling the RRT was respiratory distress, followed by hypotension. The worried criterion, or “intuition”, was equally used in almost one fifth of the calls.

Limitations of medical treatment were frequent, assigned to around one third of the RRT patients, and 30 day mortality was high at both centers: 27.7% and 29.4%, respectively.
STUDY III

Of 2,571 admissions to the general ICU at Karolinska between 2007 and 2009, 694 came from the general wards. Of these, 355 were identified and admitted by the Rapid Response Team. Compared to the conventional admissions from the wards, RRT admitted patients were older, 65 vs. 58 years, carried more co-morbidity in the form of malignancies and heart failure and presented with higher severity score, APACHE II of 25 vs. 21. The most common diagnosis for ICU admission for the RRT patients was severe sepsis, 18.3% while the conventionally admitted patients displayed a more heterogeneous spread of admitting diagnoses.

Table 5. Primary diagnosis on ICU admission, 12 most common shown for each group
Crude ICU mortality was 14.5% for the RRT cohort and 8.9% for the conventionally admitted. Multivariable regression revealed predictors of mortality to be age, acute admission and limitation of medical treatment. After adjustment, OR for RRT patients was no longer significant at 1.11 (95% CI 0.70-1.76).

Table 6. Patient co-morbidities, length of stay and outcome based on patients’ first ICU admission

<table>
<thead>
<tr>
<th>Chronic comorbidities, %</th>
<th>Conventional ICU Admission</th>
<th>Rapid Response Team ICU Admission</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>12.6</td>
<td>12.3</td>
<td>0.9</td>
</tr>
<tr>
<td>Renal failure</td>
<td>16.0</td>
<td>15.4</td>
<td>0.9</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>9.5</td>
<td>13.5</td>
<td>0.1</td>
</tr>
<tr>
<td>Heart failure</td>
<td>11.7</td>
<td>17.3</td>
<td>0.04</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>12.0</td>
<td>13.2</td>
<td>0.7</td>
</tr>
<tr>
<td>Malignancy</td>
<td>35.1</td>
<td>45.3</td>
<td>0.01</td>
</tr>
<tr>
<td>Hospital LOS Days, median (interquartile range)</td>
<td>12.5 (6–275)</td>
<td>18 (9–32)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ICU LOS Days, median (interquartile range)</td>
<td>1.2 (0.6–3.3)</td>
<td>2.0 (0.9–5.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Standardized mortality ratio based on Acute Physiology and Chronic Health Evaluation II score</td>
<td>0.51</td>
<td>0.54</td>
<td>0.6</td>
</tr>
<tr>
<td>Patients with LOMT, n (%)</td>
<td>51 (15.7)</td>
<td>73 (23.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>ICU mortality, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>29 (8.9)</td>
<td>46 (14.5)</td>
<td>0.04</td>
</tr>
<tr>
<td>LOMT excluded</td>
<td>9 (3.3)</td>
<td>14 (4.7)</td>
<td>0.2</td>
</tr>
<tr>
<td>Thirty-day mortality, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>62 (19.1)</td>
<td>86 (27.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>LOMT excluded</td>
<td>25 (9.1)</td>
<td>36 (14.7)</td>
<td>0.06</td>
</tr>
<tr>
<td>One-year mortality, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>103 (31.7)</td>
<td>136 (42.8)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LOMT excluded</td>
<td>57 (20.8)</td>
<td>73 (29.8)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

LOS = length of stay; LOMT, limitation of medical treatment.
Outcome data on conventional vs. rapid response team-admitted patients during 2007–2009.

**STUDY IV**

We examined 2 189 RRT calls in 1 818 hospital admissions between 2005 and 2010. Median age was 67 (IQR 57-77), the majority of patients had an acute admission (79.2%) and the most common reason for admission was malignant disease, followed by respiratory disease and trauma. 642 patients (35.3%) were assigned limitations of medical treatment (LOMT) and in 296 cases (46.1%) it was documented on the same day as the Rapid Response Team call. 152 calls in total were made to patients who already had a limitation in place. Among patients with multiple calls 44.6% received limitations. Patients receiving LOMT were older, had shorter hospital length of stay and carried a greater proportion of co-morbidities.
Table 7. Patient characteristics for unique hospital admissions, based on patients’ first RRT call

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>no LOMT</th>
<th>LOMT</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients, n</td>
<td>1818</td>
<td>1176</td>
<td>642</td>
<td></td>
</tr>
<tr>
<td>Age, years median (IQR)</td>
<td>67 (57-77)</td>
<td>64 (52-74)</td>
<td>74 (64-82)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Sex, female (%)</td>
<td>45.8</td>
<td>44.0</td>
<td>49.2</td>
<td>0.03</td>
</tr>
<tr>
<td>Type of admission, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical</td>
<td>55.0</td>
<td>52.3</td>
<td>60.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Acute</td>
<td>79.2</td>
<td>75.0</td>
<td>86.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hospital LOS, days median (IQR)</td>
<td>14 (7-27)</td>
<td>15 (7.5-28)</td>
<td>12 (5-25)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Multiple RRT calls, %</td>
<td>15.4</td>
<td>13.2</td>
<td>19.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Main reason for admission, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>28.0</td>
<td>25.9</td>
<td>31.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Respiratory diseases</td>
<td>13.3</td>
<td>12.0</td>
<td>15.6</td>
<td>0.04</td>
</tr>
<tr>
<td>Trauma</td>
<td>11.6</td>
<td>11.8</td>
<td>11.1</td>
<td>0.6</td>
</tr>
<tr>
<td>Infectious diseases</td>
<td>10.5</td>
<td>11.4</td>
<td>8.9</td>
<td>0.1</td>
</tr>
<tr>
<td>Gastrointestinal diseases</td>
<td>10.1</td>
<td>9.5</td>
<td>11.1</td>
<td>0.3</td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>7.3</td>
<td>6.2</td>
<td>9.4</td>
<td>0.02</td>
</tr>
<tr>
<td>Co-morbidities, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>45.7</td>
<td>41.2</td>
<td>54.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Heart failure</td>
<td>22.3</td>
<td>18.1</td>
<td>30.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>17.4</td>
<td>16.6</td>
<td>18.9</td>
<td>0.2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>16.8</td>
<td>17.2</td>
<td>16.0</td>
<td>0.6</td>
</tr>
<tr>
<td>Renal failure</td>
<td>16.7</td>
<td>14.7</td>
<td>20.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>COPD</td>
<td>16.4</td>
<td>15.8</td>
<td>17.5</td>
<td>0.4</td>
</tr>
<tr>
<td>Any co-morbidity, %</td>
<td>75.6</td>
<td>70.8</td>
<td>84.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Disposal after RRT call, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remain in ward</td>
<td>68.5</td>
<td>65.5</td>
<td>74.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Transfer to HDU</td>
<td>9.1</td>
<td>8.6</td>
<td>10.0</td>
<td>0.3</td>
</tr>
<tr>
<td>Transfer to ICU</td>
<td>22.4</td>
<td>25.9</td>
<td>15.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hospital mortality, %</td>
<td>25.6</td>
<td>6.6</td>
<td>60.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>30 day mortality</td>
<td>29.4</td>
<td>8.6</td>
<td>67.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>180 day mortality</td>
<td>43.2</td>
<td>21.2</td>
<td>83.6</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

LOS: length of stay, COPD: chronic obstructive pulmonary disease, HDU: high dependency unit, ICU: intensive care unit
Hospital mortality was 25.6% in total, 60.6% for patients with limitations and 6.6% for patients without limitations. Mortality at 180 days was 43.2% for the whole cohort, 83.6% and 21.2% with and without limitations, respectively. Although mortality did not differ, limitation of medical treatment was more common among women, 37.9% vs 33.1% for men and this was mainly due to the prevalence of specific malignancies in women of younger age.

In study I we showed that the frequency of in-hospital cardiac arrests was decreased from 1.12/1000 admissions to 0.83/1000 admissions in the first two years following RRT implementation. In study IV we found this effect to be sustained over six years with a mean of 0.82 cardiac arrests/1000 admissions.
DISCUSSION

Before I refuse to take your questions, I have an opening statement  
- Ronald Reagan

METHODOLOGICAL CONSIDERATIONS

The word epidemiology stems from Greek, meaning “the study of what is upon the people”. It can also be defined as the study of the distribution and determinants of disease frequency in human beings (55). Or more simply put, what makes us sick and why? The main objective of an epidemiological study is to identify a cause of disease, in search of effective treatments or preventive measures. However, making inferences about cause and effect is not always straightforward and choosing the accurate study design is of importance as it affects validity and precision.

Study design

Considered to be the highest scientific standard in establishing causality is the randomized clinical trial, useful to test the effect of a single intervention, such as the benefit of a drug versus placebo. Fundamental to the design is that the subjects are randomly assigned to receive the drug or not. Since proper randomized allocation keeps all other things equal, if incidence of the outcome differs between the groups the drug can be said to have an effect. However, it is not always possible, or ethical to use this design. We cannot randomize patients that are seeking care at the hospital to either receive attention from the RRT or not should their condition deteriorate. And complex interventions are by their very nature not so easily evaluated (56). Instead, observational studies (i.e. non-experimental, where nature assigns the exposure and not the investigator) can and should be used. Examples of observational studies are cohort studies and case-control studies.

In a cohort study subjects are classified based on exposure status and observed over time for outcome in the different groups. Advantages are that several different outcomes can be examined, it is suitable for studying rare exposures and time between exposure and outcome can be assessed. It is a less wise choice if the outcome of interest is rare, in which case a very large number of subjects will be needed to be able to study the outcome. Generally it is an expensive and time-consuming study design. However, in Sweden there are excellent possibilities to conduct efficient register-based cohort studies through the numerous and comprehensive health care registers at a relatively low cost. Register-based cohort studies are obviously limited to the information contained in the registers, but through the unique PIN of all residents, linkage between different registers is possible and can increase the number of variables.

Case-control studies are more feasible to use when the outcome is rare because it is based on identifying outcome status initially. Exposure status of interest is thereafter assessed in the study group (with the outcome) and the control group (without the
outcome). Health registers or subjective reports can be used although self-reported accounts of exposure status may be prone to recall bias. In this thesis, all studies are of a cohort study design. Observational studies can be further classified as either prospective or retrospective, depending on whether data collection occurs before or after the follow-up time has elapsed. We have based our four studies on prospectively collected data.

**Systematic error**

When reflecting upon the association between the exposure and outcome in observational studies, one has to consider alternative explanations that could affect the results. Without randomization all other factors are not kept equal and may in fact vary systematically between the study groups. Two principal sources of systematic errors are bias and confounding. Bias is a systematic error imposed by the study design while confounders are inherent associations between exposures, i.e. a source of error generated by nature.

**Misclassification**

All our studies rely on information from registers and patients records. If the information we use is incorrect then misclassification will occur, also called information bias. Misclassification may be differential or non-differential of either exposure or outcome. If the exposure misclassification is unrelated to the outcome, i.e. occurs in cases and controls equally then it is said to be non-differential. Differential misclassification on the other hand, is when the classification of an exposure is unequally distributed according to the outcome. Differential misclassification may either overestimate or underestimate an effect while non-differential misclassification will generally cause a dilution of the effect.

Efforts were made to reduce misclassification in Study III by validating mode of admission to the ICU through the paper RRT charts and also notes in the regular medical records. Any misclassification due to missing paper records is unlikely to be differential since it is more related to the present workload of the RRT staff than to the characteristics or outcome of the patient. Misclassification of outcome is not likely in our studies as cardiac arrests and mortality were assessed through valid and reliable registers. LOMT is however a variable that is susceptible to the risk of misclassification. It is a possibility that LOMT orders had been assigned but not correctly documented, instead either passed on as oral orders or handwritten notes. This has not been possible to control for, however in the recent years formal requirements for documentation has increased and there are clear guidelines to how limitations are documented.

**Confounding**

Confounding refers to the mixing of effects and occurs when the true association between two factors is confused by one or more other factors (57). A confounder must fulfill three basic criteria: it must be associated with the exposure, it must be a risk factor for the outcome and it can’t be an intermediary link in the causal chain between
the exposure and the outcome. Confounding is different from effect modification, where measures of effect vary across different values of another variable (57). Effect modification should be reported and described whereas confounding can be controlled for in the study design through restriction, matching or randomization, or later in the data analysis using stratification and multivariable regression analysis.

In Study I we adjusted for confounding factors such as age, sex and co-morbidities in the regression analysis as these were the confounders we judged to be clinically relevant. In Study IV, we lacked information on several factors that we could not control for, such as patients’ own wishes, socioeconomic status, the presence or absence of active relatives, whether patients were self-sufficient or not or self-perceived quality of life, so residual confounding may not be ruled out. We also found the effect of gender to be modified by age and showed this by presenting the data stratified.

Random error

Epidemiological studies aim to reflect reality by measuring a sample of the whole population and drawing conclusions on the base of that sample. This means that we have to take into account the likelihood of our sample being the result of sampling variability, leading us to incorrect conclusions. Whereas systematic errors tend to shift all measurements away from the true value in the same way, for example measuring height with a measuring tape that is consistently too short, random errors are unpredictable and can never be excluded from affecting precision to some extent. Statistical analysis can help us estimate the role of chance. Random errors will decrease with increasing sample size while systematic errors will not. A confidence interval (CI) will estimate the risk of random error, assuming there is no systematic error. It is constructed by the point estimate plus or minus its standard error (SE) multiplied by the arbitrary choice of confidence level, typically 1.96 to yield a CI of 95%. In simple terms, a CI of 95% around the point estimate includes the true estimate of interest in 19 out of 20 times. A major determinant of the width of the CI is the sample size: the larger the sample size, the more narrow the interval will be. The p-value reflects the strength of the association and the sample size, where a low p-value implies a low probability of the results having been by chance alone. Confidence intervals and p-values therefore constitute measures of precision.

In study I, more than 200 000 patients were followed for mortality at 180 days so precision was not a major problem. In Study IV, when stratifying our cohort of patients with LOMT by gender and age, the purpose was to illustrate the prevalence of LOMT and underlying malignancies in the different strata. However, assessing independent variables was then hampered by the reduced sample size and statistical analysis not possible in the subgroups.

Generalizability

After judging whether a study has internal validity, given study design, bias, confounding etc., one must consider the external validity, or generalizability of the
study. This involves considering the populations for which the results apply, i.e. are our results applicable to other populations or situations outside of our study cohort? In all studies of this thesis the source population consisted of patients admitted to the Karolinska University Hospital Solna in Stockholm, Sweden. This is a major teaching hospital and the trauma referral hospital of the entire region. Only patients that could have been exposed to the RRT were included, i.e. cardiothoracic wards and pediatric wards were not. Caution must always be taken when extending results from a single center to other settings as culture, case-mix and hospital structures may differ. In Study II, our aim was to compare our findings with another hospital in a different country and health care system in order to contribute to the concept of external validity when most studies have come from single centers.

INTERPRETATION OF FINDINGS

There is a need to realize that there are patients in general wards at risk of unrecognized deterioration, adverse events and in worst case, death. One systematic approach to improve outcome for hospital patients is through Rapid Response Systems. We evaluated the Rapid Response Team at the Karolinska University Hospital Solna and have found several important levels upon which it functions.

Study I provides evidence that the RRT has an effect on lowering the number of in-hospital cardiac arrests, with a significant 26% decrease during the study period. In study IV we confirmed this effect to be sustained over the six years the RRT had been operational. This is in accordance with other reports (49,58-65) but the first time an RRS was evaluated in a Scandinavian setting. Most of the evidence of Rapid Response Systems comes from single center before and after studies and due to the nature of the intervention, a large multicenter randomized controlled trial of RRSs is unlikely to ever be performed. Randomization on an individual level within a hospital to either receive increased vigilance of deterioration with a targeted response or not would be unethical and contamination of the control group unavoidable (66-68). One other approach is cluster randomization on hospital basis which was the study design of the MERIT study in Australia, involving 23 hospitals (69). No outcome benefit could be shown although both trial arms improved as compared with baseline. It has also been argued that the study was underpowered (70), the teams inadequately implemented (71) and that control hospitals actually adopted RRS principles and used their cardiac arrest teams for early interventions (72).

Moreover, we found a 10% decrease of overall hospital mortality even after adjusting for changes in case-mix over time. Medical patients and surgical patients not operated upon seemed to benefit the most from the system, two groups that are at high risk of an unfavorable outcome. Several other studies have shown an effect on hospital mortality (49,59,73,74) while some have not (58,63,75). A recent review of studies to date has found moderate strength of evidence that RRSs are associated with reduced rates of cardiac arrest and mortality (76). The decrease in cardiac arrests may partly be due to earlier detection and treatment of deteriorations, actually preventing cardiac arrests but partly also an effect of the
increase of limitations of medical treatment decisions that we show in study IV. The latter effect however does not explain the decrease in overall hospital mortality. We found the reduction in adjusted mortality to be associated with the implementation of the RRT, yet the number of patients seen by the RRT is not in proportion to the actual decrease of deaths. An explanation for this could be that the RRT acts on many more levels than just the number of calls delivered. The intense educational efforts that are a part of the system increase the general knowledge and awareness among the staff of failing vital signs. This in itself yields positive side-effects, providing ward staff with the tools to recognize and manage early signs of deterioration correctly (77), thus obviating the need to call the team. This is a crucial part of the system that is difficult to quantify but nonetheless has pivotal influence on how hospital patients are cared for and hence their outcome.

Opposition towards implementing a system to care for at-risk patients is partly based on notions that “this is not a problem in my hospital”, as most studies have come from single centers. In study II we explored the deteriorating ward patients in two different settings separated by distance and culture. We found that the patients detected by the RRT at both hospitals shared similar characteristics of being predominantly older, often in need of help after office hours, of potential interest to the ICU and at high risk of a bad outcome. Furthermore, in both settings the most common reasons for triggering an RRT call were respiratory distress and hypotension. There are thus patients in similar situations, with comparable presentations and outcomes both in Sweden and Australia. We have no reason to believe that these two centers should be much different from other developed hospitals in this regard. Therefore these findings, in part, refute that the issue of deteriorating ward patients would only be confined to certain settings and local contexts. Hospitals reluctant to launch an RRT based on the notion that this problem does not apply to them may be inspired to reconsider.

Study III explored patients admitted to intensive care from the general wards through two different routes, either by the RRT or in the conventional way, i.e. by direct contact from the ward physician with the ICU, as was norm before the introduction of the RRT. This study was undertaken based on the evidence that patients admitted from wards to intensive care have a worse outcome than if admitted from the emergency or operating rooms (34) and that quality of care before ICU admission has an impact on outcome (36,37). Our study is the first to examine patients admitted to intensive care by the RRT specifically, thereby exploring another aspect of the system. We found that over half of the admissions were through an RRT contact and that these patients differed from those detected by ward physicians. RRT admissions were older, carried more co-morbidities, had higher severity scores and three times more often the diagnosis of severe sepsis. Sepsis is a potentially lethal disease process that poses a major health care problem, with mortality rates well exceeding 25%, even up to 80% depending on the severity of illness (78-80). Reducing the time to diagnosis is thought to be of the utmost importance for decreasing sepsis-related mortality. Kumar et al found that mortality increases by 7% for every hour that antibiotic therapy is delayed after onset of hypotension (81), and Rivers et al showed an absolute mortality reduction of 16% when implementing early goal directed therapy before admission to the intensive care unit (82).
In our study, if looking only at crude mortality, it seemed that patients admitted by the RRT fared worse than conventional admits. One might therefore argue that the RRT offers no advantage but it’s important to recall that it is the older and more severely ill patients that are picked up by the RRT. When adjusting for confounding factors, such as age, co-morbidities and limitation of medical treatment, outcome did not differ. The RRT is thus an important pathway of finding complex patients that in spite of the severity of their illness do benefit from a higher level of care. We can only hypothesize as to how the patients would have managed had there been no RRT in place, but it is not unlikely that their recognition would be delayed and outcome impaired, given that the RRT patients present with more elusive symptoms and conditions. This was evident by the fact that admitting diagnoses set the two groups distinctly apart. It is easy to miss the signs of the early onset of a septic episode, and the Rapid Response System can be utilized to target the detection of patients in distress in general and patients with sepsis in particular.

The final aspect we explored holds ethical dimensions. Limitations of medical treatment are important for several reasons and failing to render patients limitations at the wards as appropriate is a situation in which the RRT can improve patient care. First, one must remember that setting a limit is not the same as providing no treatment at all. Limitations mean that if the patient is to deteriorate further, the up-scaling of medical care with advanced measures will not alter outcome in a favorable way. If a patient is deemed unfit to sustain certain aggressive treatments, such as cardio-pulmonary resuscitation in the event of a cardiac arrest, or endotracheal intubation and invasive ventilator therapy it should not be performed as these are also painful interventions and must be weighed against the potential benefit for each individual patient. Decisions of limitations are not taken lightly but must be taken if there is adequate reason. The RRT is often involved in these discussions as questions of appropriate level of care are frequently raised during a call. We found that a third of the RRT patients received a limitation of medical treatment at some point during their hospitalization and that almost half of these decisions were made on the same day as the call, indicating a direct involvement of the RRT. Although not an initial goal for the Rapid Response Systems several studies have reported their involvement in end of life care decisions (83-86). The RRT contributes by bringing expertise and experience to judge outcome potential (87). It is unclear whether there is a failure of ward physicians to discuss, decide and document this difficult issue on a regular basis or whether the current deterioration triggers the discussion.

Another aspect we found was that even though a patient had a previous limitation it did not exclude them from visits by the team, suggesting that the wards need support in providing comfort or appropriate treatment for patients with limitations. A patient with LOMT may in fact improve as a result of RRT actions, for example antibiotics or fluids but still retain limitations. This is highlighted by the fact that 40% of the patients with LOMT were discharged alive, although their frailty is signalled by an impaired long-term outcome. We believe it is correct that the number of limitations should be greater than actual deaths and that advance care planning should be used as a measure that can actually improve patient care (88) by focusing on what would benefit each patient the most.
In conclusion, wouldn’t it be great if patients could come to our hospital and leave unharmed? If they could get the treatment they needed, neither less nor more than is warranted by their current condition? Is it too much to ask for that patients immediately be placed at the correct level of care and then be re-evaluated as needed during their journey through the hospital? How do we achieve taking into account that biology is a dynamic process that changes over time?

In the future, perhaps we will have wireless continuous monitoring for all patients, at all times. The system will have adequate filters that sort out irrelevant noise and raise a red alert when the course of illness is taking a turn for the worse. The development may go towards neural networking that use probabilistic models to identify patients at risk (89). We may combine a panel of laboratory analysis (90,91) with automated electronic monitoring (92) in order to eliminate human error. Technical advancements are theoretically appealing, and due to our inherent eagerness to constantly evolve and improve, certainly inevitable.

However, I would like to express a personal view. I would like to propagate that we not forget basic skills. Look at your patients, talk to them and yes, touch them to feel their pulse. Lift the blanket to see if the great toe is cold (93) or if the mottling has spread beyond the kneecaps (94) – you’ll know if you are in trouble more surely than any other device will tell you. Until we have a magic marker foretelling who will improve and who will deteriorate, we need to rely on “clinical judgment”, an elusive term based on the physiological clues the patients provide us with. Assembling and evaluating these clues is something which must continue to be taught to the next generation.

The Rapid Response System does this by emphasizing the importance of basic vital signs. My hopes are that this thesis will contribute to the awareness of the deteriorating ward patients and offer a means to make their hospital stay safer. Much more work needs to be done to improve the health care system in terms of communication, education and resource allocation, and new solutions will continue to evolve. But in want of better, let’s look at our patients more often, let’s give them the care they seek but not more and let’s encourage the medical and nursing staff to be confident to practice the art of medicine.
CONCLUSIONS

1. The introduction of the Rapid Response Team at the Karolinska University Hospital Solna was associated with a significant decrease of in-hospital cardiac arrests and overall adjusted hospital mortality.

2. The issue of patients deteriorating in general wards is not an isolated phenomenon. In two diverse settings, the Rapid Response System similarly detects vulnerable patients of older age, mainly in respiratory distress and in need of attention after office hours as well as having equally high mortality rates.

3. The majority of ward patients that deteriorate to the point of needing intensive care are identified by the RRT. Although being more complex upon presentation, adjusting for age and co-morbidities reveals that their outcome is not different from those admitted through traditional channels. Importantly, patients developing severe sepsis in the wards are mainly detected by the RRT.

4. Among patients attended by the RRT, limitation of medical treatment is a frequent issue. Long-term mortality is high for patients with limitations, illustrating the severity of underlying conditions. This fact does not preclude repeated visits from the team, indicating that the Rapid Response System provides general wards with support in identifying and caring for patients at the end of life.
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- Woody Allen

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