UNIVERSITY OF STRATHCLYDE
DEPARTMENT OF BIOENGINEERING

EARLY DETECTION OF INFUSION LINE INFILTRATION: A STUDY OF DESIGN SOLUTIONS

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Abstract

Infusion pump systems are commonly used in medical practice to control the delivery of medications intravenously. The functionality and precision of these systems are paramount in ensuring patient safety and well being. Malfunctioning systems alter the amount of medication delivered to the patient resulting in over or under dosing. Despite the dangers posed to patients by malfunctioning infusion pump systems several hundred incidents of malfunction are reported to the MHRA every year. It has been speculated that a significant number of these incidents are due to line disengagement at or below the level of the coupling leading to the IV needle. Currently there is no system in place for monitoring the disengagement of the coupling mechanisms or infiltration of the medication. This lack of monitoring poses a danger to patients whereby a disengaged line will divert medication and will only be corrected when the decrease in dosage is evidenced (MHRA 2010).

A solution to the disengagement of infusion pump lines close to the level of infusion must be found to address this potentially harmful situation. The workings of several prominent brands of infusion pumps were studied, as were the luer lock system most commonly used to secure the IV needle to the infusion line. Several possible solutions were investigated. Inline pressure monitoring has been proposed as a possible means of early detection of infiltration of line disengagement. At the instance of infiltration, a drop in infusion line pressure occurs that is equal in magnitude to the venous pressure at the infusion site through *in vitro* testing. Ease of use, efficacy, integration with current systems and potential for widespread adoption in clinical use will be used as measures for the plausibility and success of the proposed solution.

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1.1 Infusion Pumps: Definition and Early Usage

1.1.1 Definitions

The following definitions are given to clarify the following work. They are written to distinguish how the terms are used in the context of this thesis and the associated lab work.

Infiltration: The removal of the cannula from the vein in such a way that the infusate flows into the surrounding tissues instead of into the vein, which has been designated as a concern in interest in the clinical environment. During infiltration the cannula remains firmly attached to the infusion line.

Extravasation: Infiltration whereby the infiltrate has toxic properties and causes a negative reaction in the subcutaneous tissue, including swelling, pain and tissue damage.

Line disengagement: The separation of the cannula and associated tubing from the infusion line in such a way that the infusate does not reach the cannula and is not infused.

1.1.2 Early Blood Infusions and Transfusions

Medical understanding in anatomy and physiology, as well as medical experimentation, evolved quickly to form the basis of modern medical practice starting in the early 1600s. The accurate description by William Harvey of circulatory physiology formed the basis of understanding required for the subsequent intravenous injection and transfusion experiments that took place in Europe. In 1658 Christopher Wren invented the first intravenous infusion device from a pig's bladder and a quill. He used his device to intravenously inject a mixture of opium, ale, wine, and liver of antimony into a dog. Remarkably, the dog survived with few effects, starting the push for experimentation with intravenous injection (Rivera, Strauss and Van Zunde 2005).

1.1.2.1 First Modern Medical Syringes

However there were several clinical implementation problems with Wren's device, namely proper vascular access, blood clotting and mechanical problems with the quill, which was difficult to fix in the vein and was neither durable nor firm. Thus Richard Lower, a colleague of Wren's designed and created new instruments for transfusion, as seen in figure 1, including the use of small, variable calibre silver pipes for vascular access to replace the difficult to use quills. The use of Lower's designs persisted and they were the beginning of modern syringes (Rivera, Strauss and Van Zunde 2005). During this time transfusion lines were often made of animal veins and very little by way of infusion pumps existed.

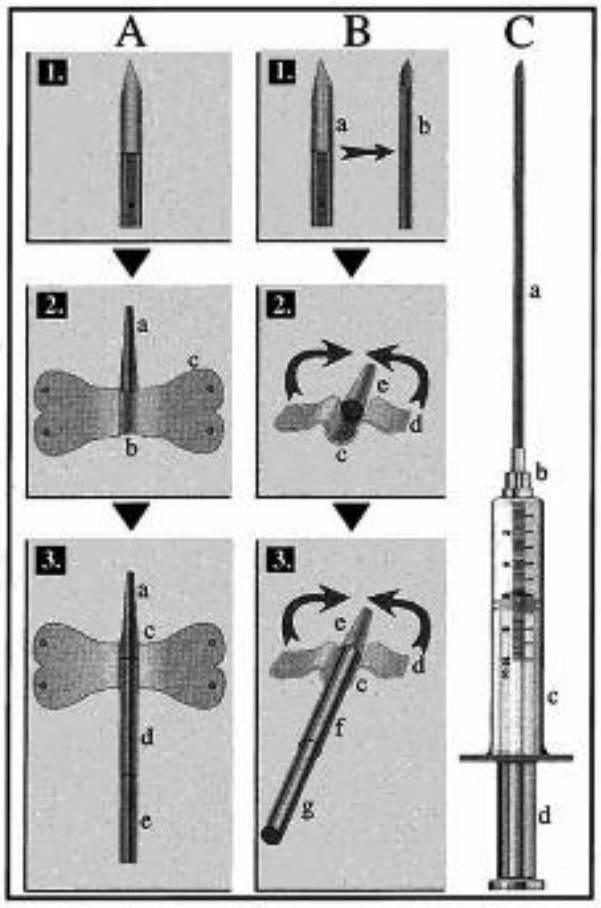

Figure 1: Evolution of Lower's IV instrument designs into modern syringe and needle (Rivera, Strauss and Van Zunde 2005)

1.1.2.2 First Human to Human Blood Transfusions

By the early 1800s the first human to human blood transfusions were being performed, albeit with mixed results. Blood clotting was a common side effect as blood typing was unknown. Dr James Blundell, the first man on record to successfully perform a human-human blood transfusion also invented two different instruments to deliver blood during infusion, the first infusion pumps. Blundell's designs, as seen in figure 2, which were gravity based, were developed with modern concerns in mind such as the careful harvesting from donors, a slow, steady infusion rate and reducing the risk of air embolism during transfusion.

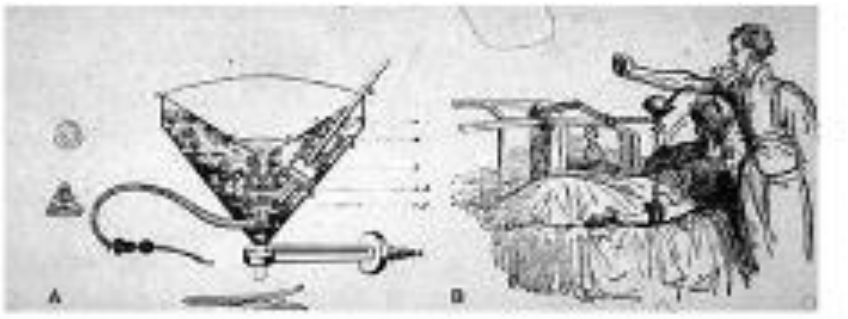

Figure 2: Blundell's infusion devices with cup and syringe (left) and elevated at height (right) (Rivera, Strauss and Van Zunde 2005)

The mid-1800s saw the development of the 'normal' saline solution for treatment of cholera by Dr. William Brooke Shaughnessy in 1832 and the perfection of the modern hollow needle by Francis Rynd in 1845. The first practical metal syringe was pioneered by Charles Pravaz in 1853 and two years later the hypodermic syringe was first used for the routine injection of narcotics in Edinburgh (Rivera, Strauss and Van Zunde 2005).

1.2 Infusion Pumps: Evolution

1.2.1 First Infusion Devices

The first infusions were done manually using syringes, making the syringe pump the oldest design for infusion therapy (Gedeon 2006). Pioneered by Christopher Wren the syringe is still a popular method of controlled infusion today, albeit with an automated delivery.

1.2.2 Early 1900s

The advent of the First World War saw a plethora of new medical devices pioneered on the battlefield and the transfusion of blood perfected (Rivera, Strauss and Van Zunde 2005). In 1933 Baxter Travenol Company, later to become one of the most recognised names in infusion therapy, commercialised the first intravenous solutions to be packaged in vacuum-sealed bottles, drastically reducing the contamination of intravenous fluids by microbial growth (Rivera, Strauss and Van Zunde 2005).

1.2.3 Post War to Modern Era

The 1950s saw the commercialisation and clinical adoption of infusion pumps on a scale not previously seen (Dorman and Buchwald 1988). The proliferation of infusion technology happened in tandem with improvements to the supporting technologies. One of the most important advances of this era was the replacement of traditional rubber infusion lines with plastic ones. However steel needles were still being used and venous access could still be problematic. The invention of the Rochester plastic needle, the first catheter, that could be directly threaded into a vein eased the process of venous access and improved patient comfort (Rivera, Strauss and Van Zunde 2005).

The 1970s gave several meaningful advances in infusion therapy. Plastic bags replaced vacuum-sealed bottles as the repository for intravenous fluids, decreasing the risk of air embolism. The precision, machine tipped catheter was smoother and more precisely formed than older models and greatly improved patient experience (Rivera, Strauss and Van Zunde 2005). Infusion pumps took a great leap forward with the invention of the wearable infusion pump by Dean Kamer. The new pump was much smaller than existing models giving patients a greater degree of freedom (Worcester Polytechnic Institute 1995). This lead directly to the invention of the diabetic insulin pump, first pioneered at the National Institute for Medical Research in London, England which cab been seen in figure 3 (The Science Museum 2012).

Figure 3: Mill Hill first insulin pump for diabetics (The Science Museum 2012)

1.3 Infusion Pumps: A Key Clinical Technology

For the last one hundred and fifty years infusion technology has been a cornerstone of medical therapy. From early cholera treatments, through life-saving blood transfusions during wartime operations, to the modern treatment of diabetes and widespread use in hospitals, infusion pumps are a key clinical technology. Infusion therapy is used to treat patients from neonatal to palliative care for the administering of fluids, medication, nutrition, and blood and blood products. It is essential that such an influential technology be designed to the highest potential to deliver the highest standard of care available.

2. Infusion Pumps: Current Technology

Infusion pumps deliver and control the flow of liquids administered intravenously to a patient. They are a commonly used medical device in the administration of medications and vital fluids in a hospital environment and are a critical piece of technology in the treatment of patients. The infusion pump system typically includes the pump itself, the liquid to be administered, the intravenous needle, and tubing line connecting the needle and the output of the pump.

The types and applications of infusion pumps will be enumerated and explored for their relevance to the current design challenge. The rate of incidence of line disengagement and infiltration, as it pertains to the current challenge, will be assessed based on incident reports from both the United Kingdom and the United States of America so as to obtain a broad idea of the prevalence of these issues. The current safety measures implemented in infusion pump design will be explored and their pertinence to the issues of line disengagement and infiltration will be assessed.

2.1 Current Uses

Infusion pumps have multiple applications in the hospital, the ambulance and at home. Hospital applications are widespread and varied and will be the focus of this project. They are used in almost all wards to deliver medications, solution (such as saline for hydration), parenteral nutrition, lipids, blood and blood products or components (Baxter 2011). The use of infusion pumps is especially prevalent in hospital wards where patients spend an extended period for treatment. Intensive care units often use multiple infusion pumps to deliver medications and nutrition to their patients when the patient may be incapable of other methods of ingestion. Infusion pumps are commonly used in surgical application for the infusion of blood or blood products to augment the blood volume of the patient and compensate for blood loss during surgical procedures. A common hospital infusion pump, the Baxter 3, is shown in figure 4. Note

the space for three infusion lines. This is common in hospital situations where multiple infusion lines to the same patient are common.

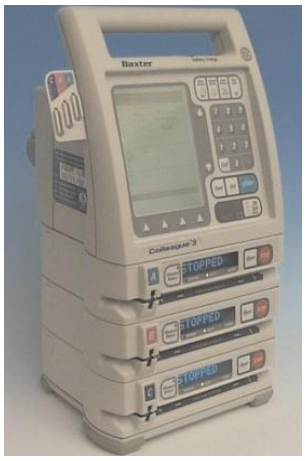

Figure 4 : Baxter Colleague 3 hospital-based volumetric infusion pump (Baxter 2011)

Ambulatory use of infusion pumps is common for the administration of fluids or blood products in the case of trauma. Ambulatory infusion pumps are smaller and more mobile than hospital based infusion pump, designed to be used in the restricted space of the ambulance and to be able to be taken to the patient if necessary. The smaller and more portable design of ambulatory infusion pumps lends them to home use, as they will have a lesser impact on the mobility of the user (Rapsilber and Camp-Sorell 1995).

Home use of infusion pumps has been increasing the last twenty-five years and now represents a $2 billion (US) industry in the United States (Laskey, Dyer and Tobias 2002). The home uses of infusion pumps are varied, and include insulin injection for diabetics, long-term courses of antibiotics for stubborn infection of those recovering from surgery, and oncology based drug regimes (Rapsilber and Camp-Sorell 1995) (Laskey, Dyer and Tobias 2002). More recent advances have allowed for the development of implantable infusion pumps that improves the mobility of the user. One such pump, the Codman 3000 which can be seen in figure 5, has been altered by a research group based in Belgium to accommodate large (16-50ml) doses and increased viscosity (23.96 mPa s) to accommodate anti-retroviral drugs for HIV treatment. This group seeks to improve upon drug compliance in HIV positive patients (Lievan Baert 2008).

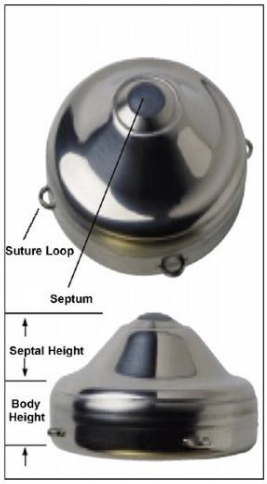

Figure 5: Codman 3000 implantable infusion pump (Lievan Baert 2008)

2.2 Types of Pumps

There are several types of infusion pumps, classified by the method of fluid control: gravity fed, positive pumping action, volumetric, and syringe (MHRA 2010).

Gravity pumps use the fluid pressure developed by the height difference between the fluid source and the patient to move the fluid down the line and into the patient. The fluid flow is controlled via a clamping mechanism that limits the flow of fluid into the patient. Positive pumping action, or elastomeric, pumps use a contracting fluid reservoir to deliver fluid at a constant rate. Powered volumetric pumps are used at higher volume and flow rate to deliver accurate and controlled fluid flow over a sustained time period. They may be further subdivided into linear peristaltic and special cassette pumps dependent on the mechanism used to supply the fluid volume. Powered syringe pumps use a screw mechanism to empty a syringe of fluid at a determined rate. They are most often used for lower volume and low flow rate applications. (MHRA 2010). Syringe pumps will be used in this project because of their widespread use in precision applications, such as neonatal wards, where infiltration injuries are most common (Tong 2011). A typical syringe pump set up can be seen in figure 6.

Figure 6: Smiths Medical Medfusion syringe pump (Smiths Medical 2011)

Infusion pumps can also be classified by how the solution is delivered. Intravenous infusions occur where the cannula is inserted into a vein, most commonly in the back of the hand, or in some intensive care cases into the neck. Other types of infusion pumps include intra-arterial pumps where the cannula is inserted into an artery, epidural pumps such as those used in childbirth where the cannula is introduced into the epidural space surrounding the spinal column, and subcutaneous infusions where the cannula is introduced just under the skin (Baxter 2011).

2.2.1 Pump Manufacturers

There are several large manufacturers of infusion pump systems. The main manufacturers include Braun Medical, Smiths Medical, Baxter and Cardinal Health. Though exact designs can vary greatly between manufacturers, the basic components and overall functionality of the pumps remains constant. This consistency allows for one pump to be chosen for the purposes of this project with the understanding that any conclusions obtained would be applicable to all pump designs. A Braun Perfusor pump was chosen for use in the experimental proceedings, as it was readily available.

2.3 Key Pump Features

2.3.1 Coupling Systems

Infusion pump output lines do not directly terminate in intravenous needles for the administration of fluid to the patient. Rather, the output line from the pump is

connected to the needle via a coupling system. This is used so that multiple pump outputs, and thus multiple medications and fluids, can be fed through the same intravenous needle, minimizing the necessity for multiple injection sites.

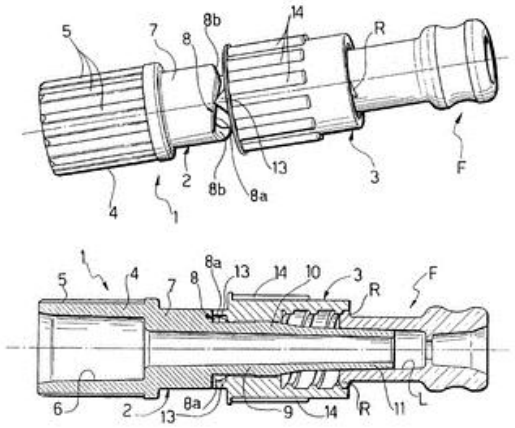

Figure 7: Luer lock coupling design (Guala 2005)

The coupling system most commonly used is the luer lock system which is depicted in figure 7. The luer lock system is a coupling device that uses a screwing mechanism to connect the pump output line to the intravenous needle. It consists of an outer movable, interiorly threaded casing that will thread onto the second line. The interior connection is immovable and tightens the upstream line until it is in firm connection with the downstream line. This external fixation of an internal connection between the lines creates a seal to eliminate fluid loss at the connection (Guala 2005). The luer lock system is used almost universally to connect intravenous needles to drug delivery lines, and is available in branched connections to allow for multiple lines to be joined.

3. Infusion Pumps: Clinical Challenges

3.1 Problems and Incidents

Over 90% of hospitalised patients receive intravenous medication, the overwhelming majority of which is delivered via infusion pumps (Breland 2010). However, infusion pump systems have recently come under fire for the number of adverse incidents associated with their use. In the United Kingdom the MHRA released a Device Bulletin in November of 2010 detailing concerns with infusion pumps systems. The bulletin, aimed at healthcare professionals, details proper pump management and operation, the training required for pump operation, and safety recommendations based on reported incidents (MHRA 2010).

In the United States the FDA launched a similar initiative in April of 2010 with the Infusion Pump Improvement Initiative. The initiative increased requirements for pre-market submissions of designs and included a letter to manufacturers reporting that many of the problems encountered were due to design flaws. The FDA also held a workshop to discuss the problems and solutions with stakeholders from academia, industry, and regulatory bodies, invested in creating new tools for more robust software development and gave public access to the ongoing discussion with a dedicated website (CDRH 2010).

The recent interest in infusion pump safety from major regulatory agencies indicates that the safety of infusion pump systems leaves room for improvement. The problems of infiltration, extravastion, and line disengagement during use, resulting in a lack of fluid delivered to the patient and damage to the surrounding tissue, was brought to the attention of the Department of Bioengineering. It was stated that there is currently no system in place to alert healthcare professionals when a line disengages at the level of the luer lock connection or when infiltration occurs. The problem, as it was presented to the Department of Bioengineering, can be found in Appendix A.

3.1.1 Incidence Rates

The MHRA received over 1000 adverse incident reports between 2005 and 2010. It is thought that these reported incidents represent only those instances where adverse consequences occurred, and that those cases where the consequences were not sufficiently important may not have been reported. Thus it is probable that a much higher rate of adverse incidents exists when all cases, not simply those that resulted in adverse consequences to the patient, are taken into account.

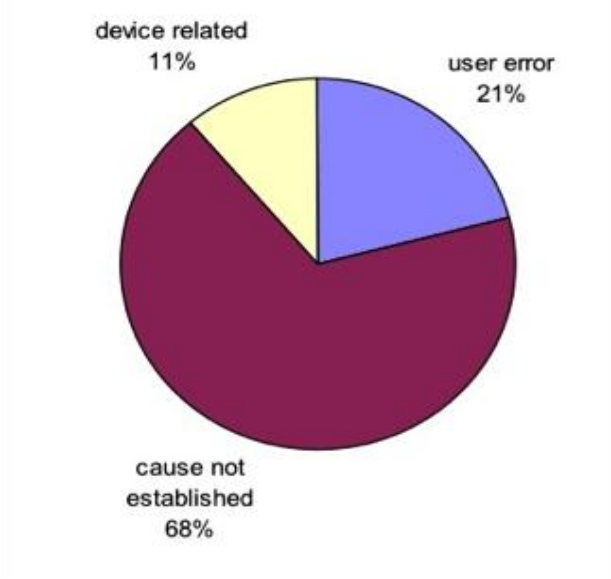

Figure 8: Outcomes of adverse incident investigations involving infusion pumps (2005-2010)(MHRA 2010)

The MHRA classified the reported incidents according to their causes, the result of which is presented in figure 8. Significantly, the majority of incidents, 68% to be precise, had no established cause (MHRA 2010). This large category of incidents is then very likely to contain the incidents of line disengagement or infiltration that are of interest. Furthermore, any incidents of line disengagement or infiltration due to patient movement, as is likely in paediatric applications, would likely be recorded as user error, as would any incidents where the lines were improperly connected, causing disengagement. It is also likely that an occurrence of line disengagement or infiltration would not be reported if it were caught and rectified quickly, or if it occurred on a line that was used for a non-vital fluid such as saline solution, where the decreased dosage

would not necessarily have an immediate or problematic effect on the patient. Combining the number of reported incidents that could be represented in the “user error” and “cause not established” categories with the possibility of unreported incidents, it is not unreasonable to conclude that line disengagment and infiltration represent some hundred cases per year in the United Kingdom.

The FDA received 56 000 adverse event reports between 2005 and 2009, and was forced to enact 87 recalls on infusion pumps during this same period. A breakdown of the causes of the adverse events was not made public, however the FDA reported three main causes: software defects, user interface problems, and mechanical or electrical failure (CDRH 2010). Line disengagement and infiltration would fall within the third category of mechanical failure of the device. Should disengagement and infiltration represent only one percent of incidents reported this would still affect the lives of more than 130 patients each year.

3.2 Infusion Pump Safety Measures

Despite the recent spotlight on the infusion pump safety issues shown by recent reports released by the MHRA and the FDA there are numerous safety features included in the current design of infusion pumps. Infusion pumps must meet guidelines set out by the ISO 9000 standard, detailing safety of medical devices, to obtain a CE mark and be used in Europe. The standards for FDA approval are similar in their safety criteria. This includes mechanically sound design and electrical safety. The device is grounded and electrically isolated from the patient. The specifics of electrical safety and design vary from pump to pump and do not impact the current area of interest in line disengagement and infiltration. For these reasons electrical safety of the pumps will not be further explored.

Of interest to the current topic of line disengagement and infiltration are the various alarms and sensors used to monitor the flow of fluid in the lines, as well as improvements in dosage monitoring and the importance of operator care. To investigate the working of these alarms a Baxter Colleague 3 pump manual was used. It can be

assumed that the types and workings of the alarms on other pumps are sufficiently similar to those of the Colleague 3 for the purposes of this report. The safety measures of interest on the Colleague 3 were those sensing the loading of the line and upstream and downstream occlusion of the line.

3.2.1 Infusion Line Loading Alarms

The functioning of the infusion pump and the delivery of the desired fluid to the patient is dependant on the line joining the pump to the cannula. The loading of this line into the pump is thus of utmost importance as well as offers a significant chance for the introduction of user error, given that the line must be loaded separately for each infusion and each use of the pump. When the line is loaded into the infusion pump a quick testing of the line is performed to ensure it is properly setup. Should the pump detect a poorly loaded line it sounds an alarm and will not allow the user to continue to set up the infusion until the line is reloaded correctly. This ensures that an incorrectly loaded line cannot be used (Baxter 2011).

3.2.2 Occlusion Alarms

Two types of occlusion alarms are used to ensure that the line remains clear of occlusions. The two types of alarms detect occlusions upstream of the pump and downstream of the pump. The alarms work on the concept of increased inline pressure associated with the occlusion of the line. Where the line runs through the pump there are two cantilevered beams with strain gauges attached and in contact with the line. When the line becomes occluded, either upstream or downstream from the pump, the strain gauge on that side of the line will register a deformation of the line associated with the increase in inline pressure when a downstream occlusion occurs and a drop in pressure when an upstream occlusion occurs. This deformation is translated into an electrical signal and compared to the minimum pressure values set by the user to detect occlusions. Should the pressure detected be greater than the limit set by the user, an occlusion alarm will sound and the pump will be shut off. The pump is shut off to ensure that a bolus of accumulated fluid is not created as this could potentially overdose the

patient when the occlusion is removed. The user must be allowed to set the limits for the occlusion alarms so as to accommodate the variation in line pressures associated with variable flow rates and fluid viscosities (Baxter 2011).

3.2.3 Intelligent Infusion Pumps

One of the more common causes of adverse drug events in a hospital setting is having an incorrect dosage administered via infusion pump. This can occur if the user inadvertently enters an incorrect dose, either from inattention or due to software errors within the pump. Given the rate of software errors occurring, as evidenced by the FDA focus on software improvements, it would be a boon to both the patient and the hospital if these errors could be readily detected (CDRH 2010). To address this issue so called intelligent or smart infusion pumps have been developed with the goals of minimizing adverse drug events due to dosage errors and improving patient safety.

Intelligent infusion pumps have increased computing power over traditional models, with the ability to connect wirelessly to the hospital network to send reports to interested personnel and to download drug libraries with information about dosing limits and drug safety. These capabilities allow the infusion pump system to monitor the doses being given to the patient and to compare these doses to the accepted limits from the drug libraries. They can alert personnel when a possible dosing error has been made, limiting adverse drug events (Breland 2010). The monitoring done by the newer smart infusion pumps, along with the increased computing power, could represent a possible advantage in detecting line disengagement and infiltration.

3.3 Early Detection of Infiltration and Extravasation

Despite the numerous alarms that are currently part of the safety features present on infusion pumps, and the potential inherent in new designs of intelligent infusion pump, there is as yet no infusion pump or associated device on the market that can reliable detect infiltration or line disengagement at the level of the cannula (Tong 2011). Current infusion pumps have only high pressure alarms that will not sound until significant, tissue damaging swelling has caused a high pressure to build at the

infiltrated tissue. High pressures from extravasation are commonly much lower than occlusions pressures, negating the value of such alarms in infiltration monitoring and detection (Tong 2011). Current detection of infiltration relies on nursing skill and routine inspections of infusion sites (Tong 2011). However it has been proven that inline pressure monitoring of infusion lines could, in theory, detect early infiltration and help prevent extravasaion injuries (Harris and von Maltzahn 1993) (Guy and Pons de Vincent 1992).

3.3.1 Definitions

Infiltration is a clinical term that refers to the unintentional leakage of infused fluid into the tissue surrounding the infusion site (Wynsma 1998) whereas extravasation refers to the infiltration of vesicant medications, or those medications that cause a toxic reaction in the body. The penetration of the infusion fluid into the perivasacular or subcutaneous space can cause tissue damage. Tissue damage is most common and most severe in infusion sites where the skin and subcutaneous tissue are thinnest (Gault 1993) (Rose, et al. 2008). These are, incidentally, also the most favourable sites for infusion, such as the forearm and dorsum of the hand and foot (Gault 1993)

3.3.2 Prevalence

The prevalence of infiltration and extravasation is hard to quantify due to the range in severity and consequences possible. Incidences of infiltration that were caught early and had no adverse effects beyond swelling and some pain may not be reported in the same manner, or with the same diligence, as those which had more severe and lasting consequences. Extravasation rates in literature range from 10 – 30 % with the accepted rates for children running as high as 58% (Rose, et al. 2008). In the United Kingdom skin necrosis as a result of extravasation injuries occur in 3.8% of neonates in intensive care units (Tong 2011). Despite this high prevalence and the risk for significant and lasting damage to the patient the research into prevention, care, and treatment of these patients, particularly children, is not extensive.

3.3.3 Injuries and Controlling Factors

Extravasation of infusion line during treatment can lead to a number of adverse clinical incidents with a wide range in severity. Though the most direct and obvious effect is the interruption of drug delivery from the infusion pump into the patient the secondary effects are often more serious, particularly with very young or weak patients (Rose, et al. 2008).

3.3.3.1 Injuries and Treatments

Extravasation injuries range from mild swelling and irritation to significant tissue necrosis. Accordingly, the methods used to treat extravasation injuries vary from elevation of the injury site and antibiotic treatments to surgical intervention (Rose, et al. 2008). Extravastion injuries are categorised according to their severity. One such classification table with corresponding symptoms can in table 1.

Table 1: Staging of intravenous infiltrates adopted from (Rose, et al. 2008)

Stage of infiltration	Features
I	Painful IV site No erythema No swelling
II	Painful IV site Slight selling (0-20%) No blanching Good pulse below infiltration site Brisk capillary refill below infiltration site
III	Painful IV site Marked swelling (30-50%) Blanching Skin cool to touch Good pulse below infiltration site Brisk capillary refill below infiltration site
IV	Painful IV site Very marked swelling (>75%) Blanching Skin cool to touch Decreased or absent pulse* Capillary refill > four seconds* Skin breakdown or necrosis*
* The presence of any one of these characteristics constitutes a Stage IV infiltrate	

Tissue necrosis often requires surgical intervention and skin grafts for treatment and can result in significant scarring. An example of tissue necrosis is shown below in figure 9. Furthermore compartment syndrome is a risk, particularly in young patient and can cause lasting damage to the limb (Tong 2011).

Figure 9: Extravasation injury resulting in tissue necrosis and removal (Rose, et al. 2008)

There are three main factors associated with increased risk of injury due to extravasation: speed of detection and treatment, age, health and nutritional state of the patient, and the amount, type and toxicity of the agent infused (Rose, et al. 2008).

3.3.3.2 Patient Factors

Extravasation injuries do not happen uniformly across all patient groups, but rather are highly prevalent in certain at risk groups including children and neonates, cancer patients, the elderly and those presenting peripheral neuropathy or decreased consciousness (Rose, et al. 2008). Early extravasation injuries are associated with pain due to the irritation caused, and the pressure asserted, by the infiltrated fluid. However in patients unable to recognise or verbalise pain, such as in neonates and patients with decreased consciousness or peripheral neuropathy, it is possible for the time prior to detection of extravasation to lengthen considerably and is generally dependant on the nursing staff for early detection (Tong 2011). Children are particularly at risk for extravasation injuries as they are not only less able to communicate pain to nursing staff

but they have poor venous integrity, decreased peripheral circulation and highly flexible subcutaneous tissue which is more prone to damage when compared to healthy adults (Rose, et al. 2008) (Tong 2011). Cancer patients are often subjected to the repeated use of veins for intravenous therapy, which can weaken veins and increase the risk of extravasation, while elderly patients often have thinner, weaker skin and veins that can be more easily damaged. (Rose, et al. 2008). The health of the tissue surrounding an infusion site will also affect the risks of extravasation and the extent of damage should it present.

3.3.3.3 Agent Factors

The injuries caused by extravasation vary with the type of fluid infused, the health and composition of the surrounding tissues and the duration of extravasation (Rose, et al. 2008). The type, toxicity and amount of fluid that leaks into the subcutaneous tissue will have a significant impact on the extent of the injuries sustained, independent of the time elapsed prior to treatment and the risk factors of the individual patient (Rose, et al. 2008).

Infused agents can be classified into three main categories based on the effects and severity of which they produce on the body. The most harmful category of agents is vesicants, which are defined as those agents likely to cause necrosis (Rose, et al. 2008). Vesicants are the most likely agents to cause severe and lasting tissue damage and skin necrosis requiring surgical treatment. Irritants are less toxic that vesicants and usually produce an inflammation reaction at the site of extravasation. Treated promptly, they are unlikely to cause tissue necrosis. Non-vesicants are the least toxic and can be absorbed into the surrounding tissues with relative speed and ease. Lasting damage is unlikely. Table 2 shows the classification of common medications as relates to toxicity and extravasation (Rose, et al. 2008).

Table 2: Toxicity classification of common infusion agents adapted from (Rose, et al. 2008)

Vesicants	Irritants	Non-vesicants

Actinomycin D Carmastine Decarbazine Daunorubicin Epinabicin Mitomycin C Mustine Vinblastine Vincristine Vindesine	Busulphan Carboplatin Etoposide Methotrexate Taxol	Melphalan Cyclophophamide Cisplatin Bleamycin Asparaginase 5-Fluorouracil
Non-Cytotoxic agents with vesicants potential		
Hyperosmolar agents	**Vasopressor agents**	**Alkaline and acid agents**
Calcium Chloride Calcium glucomate 10% Hypertonic glucose (>10%) Parenteral nutrition Sodium bicorbonate Mannitol (10% and 20% X-ray contrast media	Adrenaline Dopamine Dobutamine Noradrenaline Vasopressin Prostoglandins	Erythromycin Diazepram injection Mancomycin Phenytoin Aminophylline Acyclovir Amphotericin B

3.3.3.4 Detection and Treatment

The time elapsed prior to detection and treatment of infiltration and extravastion has a significant impact on the severity of the injury as well as the prescribed treatment (Tong 2011) (Rose, et al. 2008). When mild infiltration is treated immediately, 89% of patients see no lasting adverse effects and do not require surgical intervention (Larson 1982). However, if extravastion is allowed to progress to later stages tissue necrosis and surgical intervention become increasingly likely. Thus the early detection of infiltration and extravastion is essential for the prevention of potentially severe and lasting tissue damage in at risk patients.

4. A Search for a Solution

Current protocols for the detection of extravasation rely on the patient to communicate any pain associated with infusion sites, if possible, and the regular inspection of infusion sites by nursing staff. In neonatal wards, where extravasation rates are highest, injuries can develop more quickly, and patients are unable to communicate the source of pain nursing protocols demand hourly inspections of the infusion sites for early signs of extravasation and infiltration (Tong 2011).

Despite the protocols in place for the detection of extravasaton and infiltration the incidence rates do not show signs of dropping. It was proposed that an engineering solution might be applied to this problem to help in the early detection of line extravasation, infiltration and line disengagement at the level of the cannula. The original problem definition, as it was presented to the Department of Bioengineering, can be found in Appendix A.

The idea that an engineering solution exists and could help with the early detection of infiltration and line disengagement assumes that there exists a single or a set of characteristic signs of line infiltration and disengagement that could be monitored and used to sound an alarm when a problem is indicated to have occurred. Though extravasation and infiltration injuries present several sets of symptoms these symptoms occur after a time interval has elapsed, when injury may already have occurred, and they are likely to be picked up in the inspection of cannula sites by nursing staff. Furthermore any signs of injury from infiltration or extravasation would not be present at a disengagement of the infusion line.

It has been indicated that inline pressure in the infusion line will undergo changes during the early stages of infiltration (Guy and Pons de Vincent 1992). Furthermore, there is a pressure associated with the blood flow in the vein into which the cannula is inserted. The inline pressure in the infusion line is a result of the resistance to flow of the line, connectors and cannula, the height differential between the infusion source and the insertion site, and the venous pressure at the site of infusion. The typical

pressure breakdown for adults and neonates, respectively, is shown below in table 3. Note that the pressure drops shown in table 3 are average pressure drops as pressure would be dependant on flow rate and fluid viscosity. The average drops were used to determine the level of precision necessary and the scale of the expected values during experimentation.

Table 3: Breakdown in inline infusion pressures adapted from (MHRA 2010)

Pressure Drops in Infusion Lines		
	Pressure Drop (mmHg)	
Source of Pressure Drop	Adult	Neonatal
Administration Set	1	<1
Cannula	100	10
Filter	10	1
Venous Pressure	30	10
Total	141	22

As can be seen from the table above, the venous pressure varies from 10mmHg to 30mmHg depending on the patient. The venous pressure is always present, its source the flow of blood thought the vein where the cannula is situated. At infiltration of the line the cannula slips out of the vein to infuse fluid into the surrounding tissue. This should, in theory, be associated with a pressure drop equal to the venous pressure in the vein minus the pressure exerted on the cannula from the surrounding tissues. This pressure exerted on the cannula from the tissues can be assumed to be small, given that the infiltration of infusion fluid in the tissues does not raise the pressure a considerable amount prior to significant injury (Rose, et al. 2008) (Tong 2011). This can be assumed as occlusion high-pressure alarms are not tripped when infiltration is present. Thus infiltration should be associated with an inline infusion pressure drop approximately equal to the venous pressure at the infusion site.

The disengagement of the infusion line, so as to leak infusion fluid out of the line prior to reaching the patient, should be associated with a pressure drop equal to the sum of the resistance pressure in the line below the point of disengagement and the venous pressure. Given the relatively low resistance to flow in the infusion line, disengagement

of the infusion line should be associated with a pressure drop approximately equal to the venous pressure at the infusion site. However should disengagement above the cannula occurs than the expected drop in pressure would be equal to the sum of the pressures associated with the venous pressure and the pressure due to the cannula.

Accordingly, infiltration and disengagement of the infusion line should both be able to be detected through inline pressure monitoring in the infusion line. A pressure drop equal to the fluid pressure in the vein should indicate one of these two problems. A possible design to detect infiltration and line disengagement will be proposed on the basis of inline pressure monitoring. The theory of infiltration detection through pressure monitoring will be tested experimentally and suggestions given for engineering solutions to early detection of infiltration and line disengagement.

5. Design Theory

5.1 Design Challenge

The lack of automated detection of line disengagement and infilatration with the use of infusion pump systems has been presented as a detriment to patient care. Given the widespread use of infusion pump systems and the number of reported adverse incidents each year, this lack of detection is unacceptable. The design challenge to be met is that of creating a system of early detection for line infiltration and extravasation for infusion pump systems. Two possible types of solutions exist: solutions that would inhibit line decoupling and extravasation and solutions that would alert users to infiltration and extravasation.

5.2 Design Generation and Assessment

Several design possibilities must be generated to ensure that the final prototype is of robust design and represents the best possible solution to the presented challenge. Research of the environment in which infusion systems are used will be conducted via visits to two hospitals in the Glasgow area. During these visits consultations will be made with both the healthcare professionals who use the pumps daily and the medical engineers who service the pumps. This is to ensure that the proposed designs will meet the requirements of all users.

The choice of this final design will be done in two ways, by assessing the design based on restrictions and criteria placed upon it and by testing any plausible designs that succeed in the first assessment.

5.2.1 Clinical Observations

To obtain insight into the clinical environment in which the proposed design would be used two hospital visits were taken to the Intensive Care Unit and Medical Physics Department in the Royal Alexandra Hospital and to the Neonatal Intensive care Ward at Yorkhill Hospital, both in Glasgow, Scotland. The two visits helped to form

several key ideas about the environment in which the design would be used and the design considerations to enhance the likelihood of clinical adoption.

The immediate bedside area in both the adult and neonatal ICU wards showed a preponderance of medical equipment both for treatment and for patient monitoring. Multiple infusion pumps were used, in conjunction with other medical devices, resulting in a high number of lines making their way to the patient, be they intravenous lines, feeding tubes or monitoring lines. The amount and complexity of the medical equipment, the use of multiple infusion pumps and associated lines all trying to access the patient reinforced the necessity for a small, simple device that could be readily used with little training and that integrated seamlessly with existing technologies. The nursing staff and doctors already have a complicated and busy job monitoring the patients and any device introduced into this environment should be specifically designed to simplify their job without causing undo complications.

5.2.2 Design Restrictions

The design that answers this challenge must meet the following restrictions for maximum efficiency:

- The proposed design will be able to detect line disengagement at or below the level of the luer lock connector.
- The proposed design will be able to detect infiltration of the cannula from the vein.
- The proposed design will alert the user to the detection of either line disengagement or infiltration.
- The proposed design will be able to function with all major existing infusion pump systems with little to no adjustment required.
- The proposed design will be simple to set up and use.
- The proposed design will not interfere with any other functions of the infusion pump system.

- The proposed design will meet the criteria for CE mark approval.
- The proposed design will be able to be mass-produced.

5.2.3 Design Criteria

The design criteria chosen were selected so as to ensure that the proposed solution would be usable in a clinical environment with existing infusion pumps and their accessories and to maximize the possibility of clinical adoption. Any design generated will be assessed not only on its ability to meet the above restrictions to design but will be judged on how well it adheres to the following criteria:

- Reasonably low cost of manufacture
- Ease of use
- Sensitivity to line disengagement
- Sensitivity to infiltration
- Robust design
- Ease of sterilisation
- Few false positive alarms
- Potential for clinical adoption
- Simplicity of design
- Small size

Two further criteria that fall within the category of "potential for clinical adoption" must be assessed in order for the chosen design to present a possibility for successful commercialisation.

Work with existing infusion pumps: The proposed design must not be pump-specific but should be able to work with both volumetric and syringe pumps from all manufacturers. This will help to ensure maximum clinical adoption. Infusion pump design is not standardized across manufacturers, nor is the type of infusion pumps used

in hospitals across Scotland. Thus to maximize the market potential of any solution, specificity to any one pump design of manufacturer must be avoided.

Though there are significant variations in the design of infusion pumps based in part upon the intended use and the preference of the manufacturers, it is shown that the workings of the pumps are significantly similar to allow for the design of any new measure to be primarily based upon the use of one pump, and that it can later be altered slightly and with ease to suit application with other pump designs. For the purposes of this report the Braun Perfusor syringe infusion pump has been chosen for in-depth investigation due to its availability for study and common use in hospitals in the United Kingdom.

Minimal modification to clinical set up: Infusion pumps are used throughout the hospital, often in conjunction with other equipment or in multiple pump set ups. This can lead to a complicated set up and large number of lines connected to the patient. To further complicate this set up with modifications required to detect infiltration could create difficulties for the nursing staff in adopting the proposed solution. Furthermore, any solution that required a complicated or unknown set up would require training of the appropriate staff and could be rejected if deemed more complex than reasonable for the prospective benefits.

5.2.4 Design Assessment

Through the considerations of the design criteria, and prioritizing a simplistic design, it was decided that a solution whereby the pressure change in the line created by the disconnection of the line or by the displacement of the cannula would be the preferred solution. This decision having been made, it became necessary to determine the optimal way to detect this change in pressure.

5.2.4.1 Inline vs External Pressure Sensors

The first choice to be made in the selection of a design was to choose how to detect the change in pressure created by extravasation, through inline or external detection methods. Inline methods are those in which the sensor is placed inline with the

flow of fluid from the infusion pump to the patient, a schematic of this type of set up is shown in figure 10.

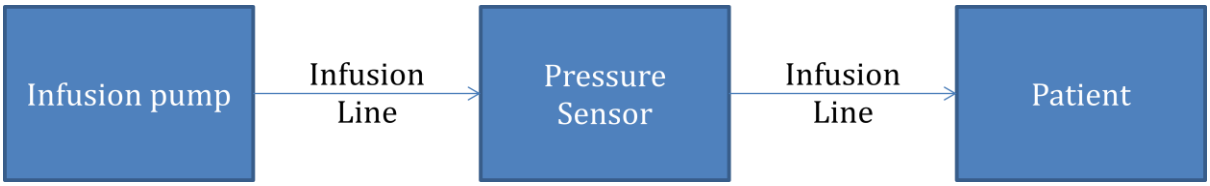

Figure 10: Schematic of inline pressure sensor

External methods are those that are not situated on the main line, but rather use a secondary measure to detect the desired pressure change. A schematic of an external sensor set up can be seen in figure 11.

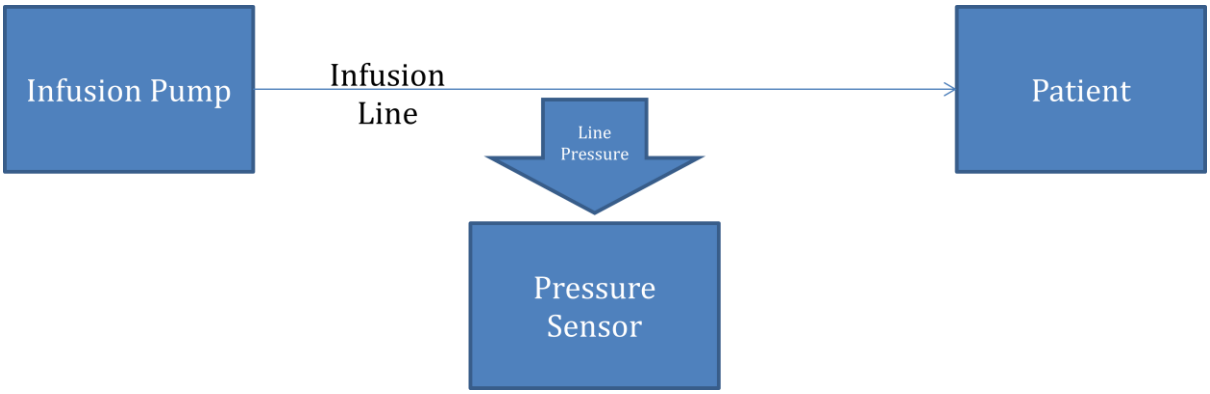

Figure 11: Schematic of external pressure sensor

5.2.4.1.1 Inline Pressure Sensors

Inline sensors are the most direct method of measuring the inline pressure changes created by extravasation and can be used to easily monitor changes in infusion pressure (Guy and Pons de Vincent 1992). Direct measurements minimize the possibility of measurement error and the accuracy and sensitivity of the measurements taken will directly correspond to those of the instrument used to take the measurement. Furthermore, the use of inline pressure sensors has been proven an effective method of detecting small pressure changes in infusion lines (Harris and von Maltzahn 1993) (Guy

and Pons de Vincent 1992). This indicates a high likelihood of success in extravasation detection should inline pressure sensors be used.

Despite the advantages in sensitivity, accuracy, simplicity of design and previous use in infusion lines, the use of inline pressure sensors does pose several challenges where commercialization and clinical adoption are concerned. The primary challenge in the development of any new medical device lies in meeting the standards and regulations imposed by the MHRA for a CE marking. Inline pressure sensors would by nature come into contact with the fluid being infused into the patient. This would require a completely sterile device that would not affect in any way the fluid passing though it and into the patient. Proving the sterility and inert nature of the device, as well as its efficacy, would require clinical trials and adherence to MHRA guidelines (Communities 1993).

Furthermore, given that inline devices would come in contact with the fluid passing though the infusion line, any design using an inline pressure sensor would by necessity be a single use, disposable device so as to eliminate the possibility of cross contamination between infusions. In designing a disposable device cost and ease of manufacturing become increasingly important design factors.

Finally, any inline design would have to connect directly to the infusion line. This would best be achieved using fasteners and lines already in use in clinical settings so as to minimize the training associated with the device and to maximize clinical adoption. This limits the design possibilities of an inline device to those that adhere to current clinical practice and design.

5.2.4.1.2 External Pressure Sensors

External pressure sensors use indirect measurements to track changes in the infusion line pressure by identifying a secondary property that changes with a change in line pressure. The changes in the secondary property are tracked and these are correlated to the changes in line pressure so as to give an approximation of line pressure. An example of a secondary property that could be tracked by an external pressure sensor is

line diameter. The pressure exerted on the walls of the infusion line is directly related to the fluid pressure in the line.

The advantages of using an indirect measurement system for detecting infiltration with infusion pumps are associated with the lack of contact between the infiltration detection device and the fluid in the infusion line. This would decrease the requirements for absolute sterility and inert materials as the patient would not come in contact with any part of the device. This would also potentially make it easier to obtain a CE mark as the clinical trials and required documentation may not be as rigorous (Communities 1993).

Indirect methods of measurement such as the one explained above introduce more sources of error than direct measurements as they rely on secondary properties, increasing the complexity of the measurement system and the possible sources of error. This decreases the sensitivity of the measurement system, which could make it difficult to measure very small changes in line pressure. No studies have been published that used an indirect measurement of line pressure to detect infiltration or small changes in line pressure. Indirect measurements are currently used to detect line occlusion in infusion pumps, such as in the Braun Infusomat and Perfusor pumps and the Baxter Colleague 3 pumps (Braun Hospital Care 2001) (Braun Hospital Care 2001) (Baxter 2011).

6. Potential Designs

Several potential designs were explored that conformed to the required design specifications. The most practical designs are shown below with their associated advantages and disadvantages.

6.1 External Ring Design

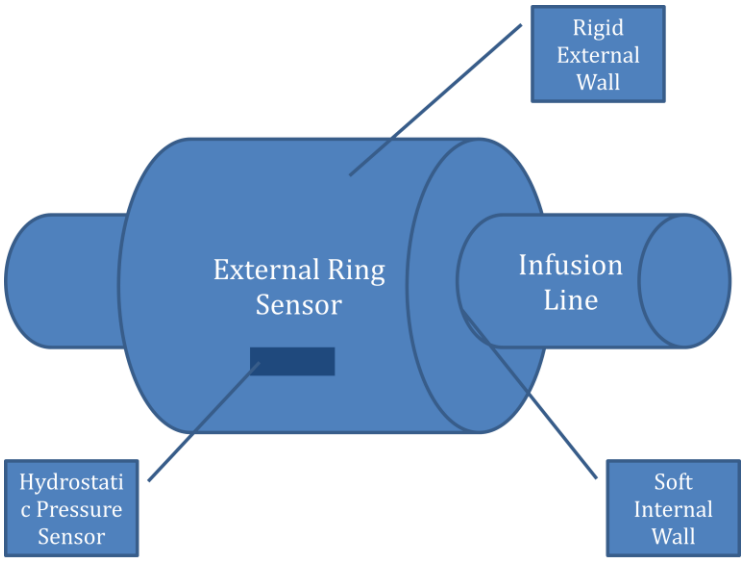

Figure 12: Schematic of external ring design

This design, an outline of which is depicted in figure 12, would consist of an external fluid filled ring that would fit snugly around the infusion line in use. Inside the fluid filled ring would be a hydrostatic fluid pressure sensor. The inner surface of the ring would be made of a material with a low modulus of elasticity and the side and outer walls would be rigid. The non-rigid walls of the line will expand with increased line pressure according to the equation:

$$\Delta P = \frac{E h_0 r_0}{2}\left[\frac{1}{\Delta r^2}\right]$$

where :

ΔP = Change in line fluid pressure

E = Elastic modulus of the infusion line

h_0 = Thickness of infusion line wall

r_0 = Original radius of infusion line

Δr = Change in radius of infusion line

The change in the radius of the infusion line, Δr , would be calculated using the change in hydrostatic pressure measured by the external pressure sensor and the corresponding change in line pressure calculated from the above equation (Waite and Fine 2007). The change in radius of the infusion line would cause an increase in hydrostatic pressure in the external ring as the internal wall of the ring was compressed and the outer walls, being rigid, limit expansion. The hydrostatic pressure sensor would than be used to measure the change in hydrostatic pressure and calculate the corresponding change in radius and ultimately the change in infusion line pressure.

6.1.1 Advantages

The external ring design would not contact the infusion fluid that would be contained inside the infusion line. This would eliminate the possibility for contamination and decrease the safety requirements for the infiltration detection design. Furthermore the flow of the infusion fluid would not be interrupted and the length, size and other properties of the infusion line would remain unchanged. This design could easily be added to existing lines and, as it fit over the line, would be compatible with all pumps. Furthermore this design would allow for reuse of the same device multiple times as there is no chance of cross contamination. This would ease the low cost requirement as hospitals may be inclined to spend more money on a reusable product than on a single use design.

6.1.2 Disadvantages

The external nature of the design necessitates an indirect measurement of the infusion fluid pressure. This design actually measures a tertiary parameter, the hydrostatic pressure inside the ring, to ascertain the change in pressure in the line. This

would allow for significant sources of error and would limit the sensitivity and accuracy of the pressure monitoring. Furthermore, this design assumes that all infusion lines have identical wall compliance as the governing equation correlates changes in wall diameter to pressure changes though modulus of elasticity and wall thickness. Should the wall compliance of infusion lines change with the type or size of infusion lines than the proposed design would not work without some method of calibration. This would dramatically increase the complexity of both design and operation of the device.

The external nature of this device increases its susceptibility to measuring changes in hydrostatic pressure not caused by changes in infusion line pressure. Movement in the line, atmospheric pressure changes or changes in the temperature of the environment could all affect the hydrostatic pressure read in the ring sensor. This could lead to false alarms or lack of detection of infiltration.

6.2 Inline Bladder Design

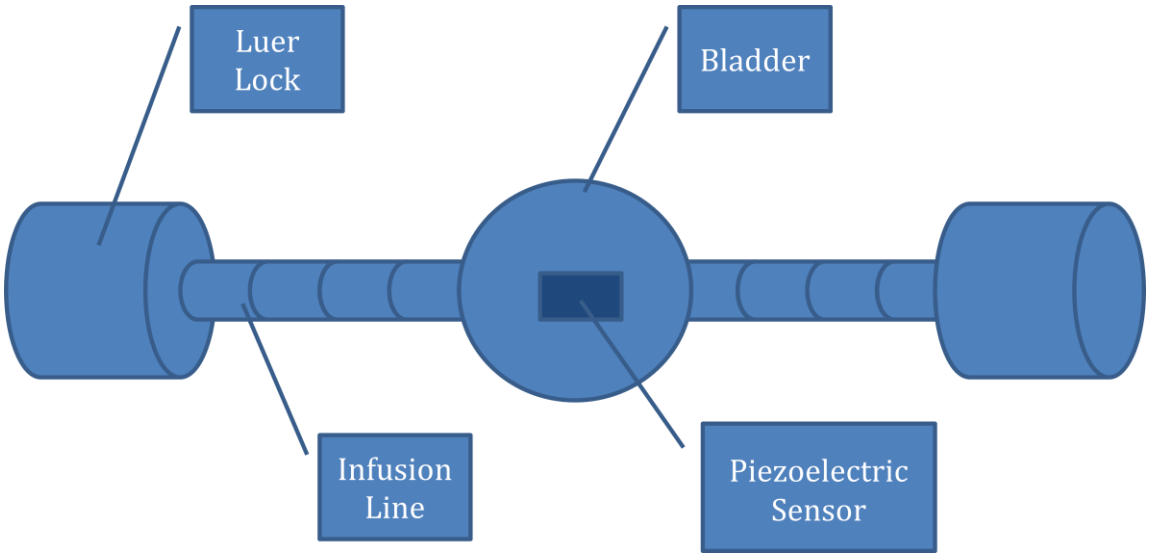

Figure 13: Schematic of inline bladder design

This design, depicted in figure 13, would consist of a length of infusion line fitted with a wider, high compliance, bladder section and external casing that would be fitted onto the infusion line just prior to the connection of the catheter. This length of additional line would be attached to the line and to the catheter on either side via luer

lock. The bladder itself would fill with infusion fluid and its size would be dependant on the fluid pressure in the infusion line. A piezoelectric sensor would be attached to the outside surface of the bladder and would measure the change in size of the bladder though the strain on the bladder walls. The whole of the bladder and sensor would be contained in a rigid casing to minimize the possibility of other forces acting on the bladder to exert strain on the walls. Assuming a roughly spherical bladder, the size of the bladder would correspond to the inline pressure though the following equation for a thin walled pressure vessel (University of Colorado Department of Engineering 2012):

$$\Delta R = \frac{\Delta \epsilon E 2t}{\Delta P}$$

Where:

R= radius of the bladder

E = modulus of elasticity of bladder walls

t = thickness of bladder walls

P = internal pressure

ε = strain on the bladder walls

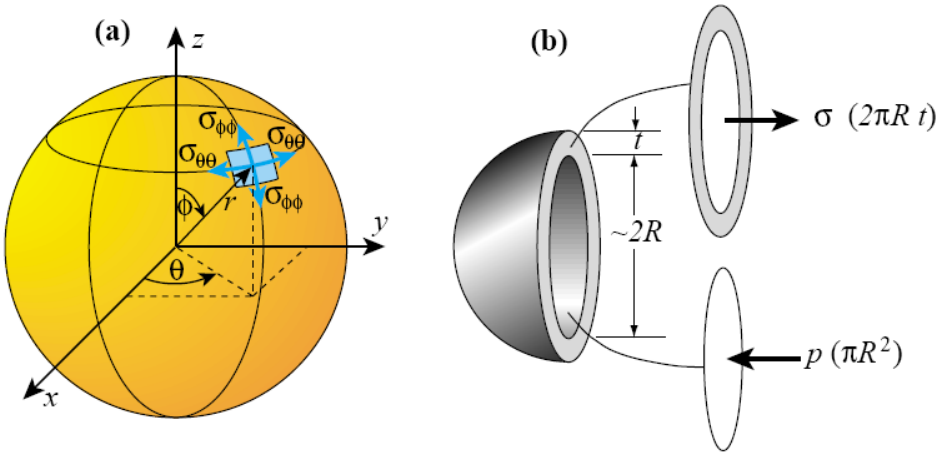

Figure 14: Stress analysis on spherical thin-walled pressure vessel (University of Colorado Department of Engineering 2012)

Figure 14 shows the forces that would be present on the bladder walls. The change in strain, $\Delta\epsilon$, would be measured by the piezoelectric sensor on the outside of the bladder, and the corresponding change in pressure, ΔP, could be calculated.

6.2.1 Advantages

The inline bladder design is a small design that works with existing standard fasteners (luer locks). Its small size will cause minimal clutter and disruption in clinical use and it is compatible with all existing systems and all line sizes. This would encourage clinical adoption of the model. The size and compliance of the bladder could be calculated to optimize the sensitivity of the design. Piezoelectric sensors are readily available and can be found in small sizes and with high accuracy and sensitivity.

6.2.2 Disadvantages

The inline bladder design uses indirect measurement, measuring the secondary parameter of bladder wall strain. While this is one degree closer to the source parameter than the external ring design it still suffers from the disadvantages inherent in an indirect measurement system. This design also lengthens the infusion line which will increase the resistance to flow, albeit slightly, and could be inconvenient in intensive care situations where multiple infusion lines are used.

As the interior of the bladder and the associated line and luer locks come into contact with the infusion fluid, sterile and inert, medical grade materials must be used throughout all components of the design. The contact with the infusion fluid would also necessitate a disposable product so as not to cross-contaminate lines through reuse. This demands a low cost of production to make the option economically viable.

6.3 Luer Lock Pressure Sensor Design

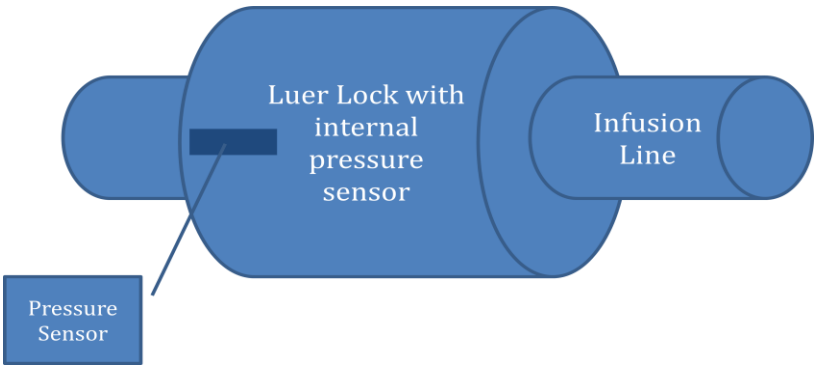

Figure 15: Schematic of luer lock pressure sensor design

A luer lock-fitted pressure sensor design, similar to the schematic shown in figure 15, would comprise a high sensitivity, high accuracy, low pressure, pressure sensor fitted into a luer lock connector. This design would directly measure the inline pressure in the infusion line and could be directly connected at any point in the infusion line given the universal use of the luer lock system. Such pressure sensors as required can be obtained from the German manufacturer SensorTechnics (SensorTechnics 2010). See Appendix B for catalogue of products.

6.3.1 Advantages

The luer lock pressure sensor design is a small, self-contained design that will work with all existing systems due to the ubiquity of the luer lock connector in clinical practice. This would greatly increase the likelihood and ease of clinical adoption, as use would require simply adding luer lock, with pressure sensor inside, to the infusion line. This design uses a direct measurement of the inline pressure though the luer lock which would maximize accuracy and sensitivity of the measurement. The accuracy and sensitivity of the pressure measurement would be completely dependant on the characteristics of the sensor used. The HMA line of pressure sensors from SensorTechnics has appropriate pressure ranges for this application (SensorTechnics 2012).

6.3.2 Disadvantages

This design requires the infusion fluid to pass though the luer lock and pass the pressure sensor prior to entering the patient. To obtain a CE mark this will require medical grade materials and a completely sterile product that must be disposable after one use. This will impact cost considerations for the design. The placement of the luer lock will impact the operation of the design. Optimally the pressure sensor would be placed directly preceding the catheter so as not to be affected by movement in the line and the resistance offered by the infusion line after the luer lock.

The pressure readings of the luer lock could be affected by motion in the infusion line, by bolus, or by pulsatile flow. Minimizing these events by careful placement of the device would ensure maximum efficientcy in detecting extravasation. The software associated with the device to detect extravasation would also be required to differentiate the pressure changes cause by motion with those caused by extravasation.

6.4 Design Choice

In contrasting the respective advantages and disadvantages of inline and external pressure monitoring designs there appear to be two main considerations: the required disposability of inline designs and the inherent compromises on accuracy of external designs. Though external designs have undisputed benefits in the possibility of a reusable design, it has not been proven that they would be able to accurately detect the small pressure changes associated with infiltration. Changes of only 10 mmHg would cause only very small increases in the radius of the silicone infusion line. Furthermore, the variety in the compliance of the silicone rubber tubing between manufacturers and the variations in wall thickness available in silicone rubber tubes would demand a lengthy calibration process for each use. These drawbacks could be somewhat compensated using a bladder design. However the bladder design, being in contact with the infusate, does not possess the advantages on reusability. Given the uncertainties associated with the external ring design an inline design was chosen. The smaller size and more direct measurements of the luer lock based pressure sensor design recommend

it over the bladder design, as does the previous body of research which indicates that the theory behind the design is sound (Harris and von Maltzahn 1993). Thus experimentation will be done to prove the validity of the theory behind the luer lock based pressure sensor design.

7. Experimental Hypothesis

Previous work in 1992 (Guy and Pons de Vincent 1992) and 1993 (Harris and von Maltzahn 1993) has shown that infiltration in infusion lines creates characteristic changes to the inline pressures recorded.

Guy and Pons de Vincent proved the ability to monitor inline pressure changes in infusion lines. They monitored 18 neonatal patients in a clinical environment over the course of three months. The line pressure measurements obtained clearly showed that inline pressure monitoring could be used to identify clinical incidents that would affect the patient. Line occlusions and infiltration were both found to be distinguishable by observing the changes in infusion line pressure (Guy and Pons de Vincent 1992).

Harris and von Maltzhan proved that a mathematical model could be used to predict the changes in infusion line pressure in various flow scenarios. The scenarios modelled included line occlusion, proximal and distal line kinks and infiltration. The model they created, based on a third order system, was able to correctly discern the type of situation occurring with a 92% reliability (Harris and von Maltzahn 1993).

Infiltration and line disengagement will each cause characteristic pressure changes in the infusion line pressure. Correctly monitored, these changes can be used to detect infiltration before pain or visual symptoms become apparent. It is expected that the simple experimental trials performed will confirm these findings. The pressure drop associated with infiltration is expected to be found equal in magnitude to the venous line pressure and to occur within a predictable time interval. The pressure drop associated with line disengagement will not be measured. However if it is proven that pressure monitoring can correctly identify infiltration, it would be recommended that further study on both infiltration and line disengagement be undertaken.

8. Experimental Design

The design restrictions and criteria, when applied to the proposed designs, indicated that an inline pressure sensor, of the type shown in the luer lock pressure sensor design above is the most promising design. To prove the potential efficacy of this design two things must be proven. First, that inline pressure can be used to reliably detect extravasation, and secondly that a pressure sensor of the required size, sensitivity and accuracy could be inserted into a luer lock connector without significantly impeding flow in the line.

To test the theory that extravasation in an infusion patient could be detected by an inline pressure sensor an *in vitro* experimental procedure was conceived and built. The experimental set up consisted of a fluid pumping circuit to simulate the fluidic parameters of the local venous environment into which the infusion takes place (hereafter called the venous circuit) and of an infusion line that infused into the venous circuit. A schematic of the set up can be seen below in figure 16.

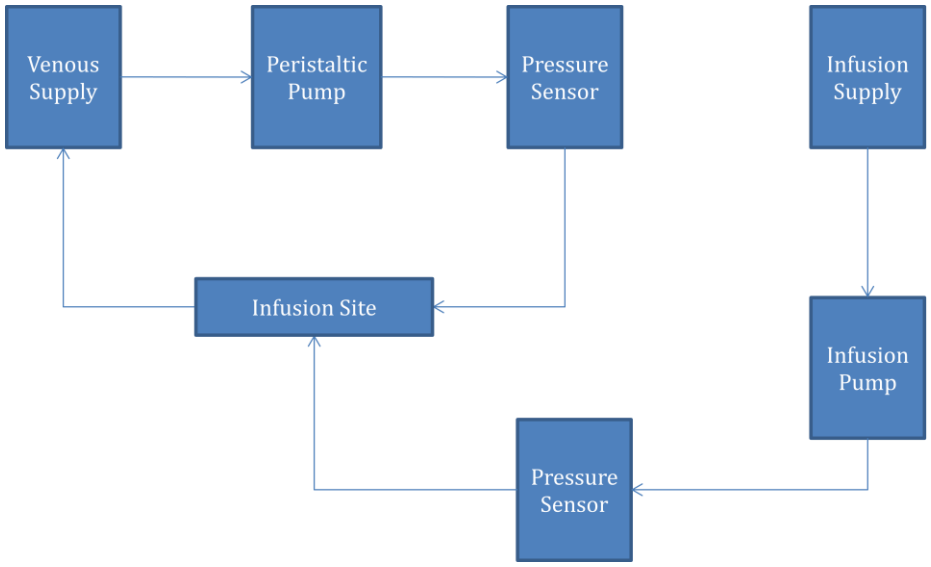

Figure 16: Schematic of experimental set up

8.1 Infusion Pump

A Braun Perfusor syringe pump was used in the experimental set up. The pump was supplied to the Department of Bioengineering courtesy of Professor George Corner, Head of Instrumentation at Ninewells Hospital and Medical School in Dundee, Scotland. An investigation of the minutiae of the pump's design will not be done here, as it can be obtained from Braun should it be of interest. The purpose of the experimental set up was to prove the efficacy of inline pressure monitoring in detecting extravasation, so the type of pump used should not affect the experimental results. However the generalities of the pump will be given below.

8.1.1 Braun Perfusor Syringe Pump

The Perfusor syringe pump is marketed as a transportable syringe pump that is suitable for liquids used in infusion therapy and nutrition of patients. The Perfusor is a high precision pump that is compatible with a range of syringe sizes and manufactures. During the experimental use of the Perfusor pump for the purposes of detecting extravasation in a laboratory setting, a 60ml syringe with a luer lock connector to the line was used with the pump. The pump is designed to be used in a clinical setting and is compatible with multiple pump setups. This is due to the smaller size of the syringe when compared to the infusion fluid bags used with volumetric pumps and the higher degree of precision possible in a syringe pump when compared to a volumetric pump (Braun Hospital Care 2001).

The functional parameters of the Perfusor pump are given as (Braun Hospital Care 2001):

- Infusion Volume: variable and dictated by syringe volume, in this case up to a maximum of 60 ml
- Infusion Rate: 1 – 999 ml/h (though more often used at low infusion rates)

8.2 Venous Circuit

8.2.1 Setup

The venous circuit is a simple circuit designed to mimic the flow rate and pressure of a vein that would be used as in infusion site. It was decided to model the venous circuit after a vein in the back of the hand, a common site for infusion. The model schematic set up is shown in figure 17.

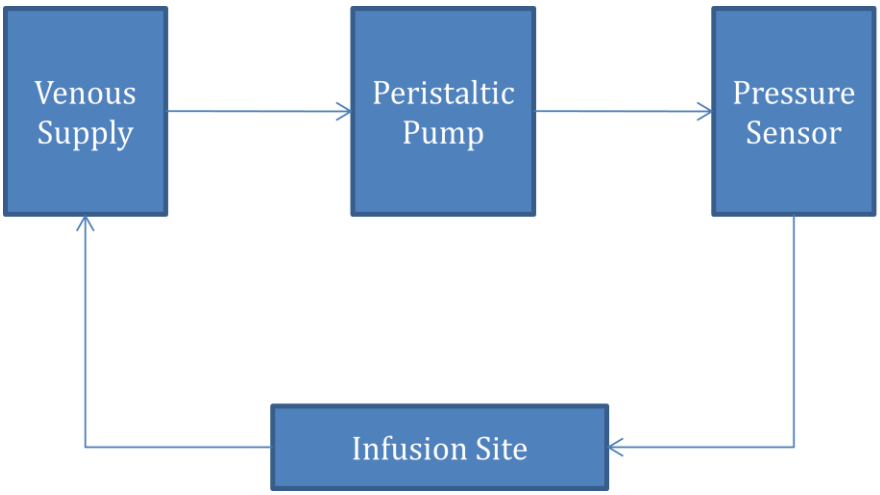

Figure 17: Schematic of venous circuit

8.2.2 Flow Parameters

The flow parameters of the venous circuit were set up to mimic the most difficult set of parameters found in a clinical setting, using the smallest flow and pressure values available. This corresponds to venous flow parameters for paediatric patients. Should extravasation detection prove possible using inline pressure monitoring in a situation representing paediatric applications than it can be reasonably extrapolated to apply to adult patients as well. However the inverse would not necessarily be true as a system that can detect changes in the high flow and pressure situations associated with adults would not necessarily be easily modified to adapt to paediatric applications. Thus the flow parameters used in the venous circuit were:

- Inline flow pressure ~10mmHg (MHRA 2010)
- Inline flow velocity of 0.5-7.7 cm/s (Silverman and McGought 1971)

Silverman and McGough examined the effect of certain medications on venous flow velocities. The range of flow velocities varied widely from individual to individual with an average velocity of between 2 and 3 cm/min. Their experimental results can be seen in figure 19. The research by Silverman and McGough was performed on adult women. As it was decided to mimic a paediatric application during experimentation, as smaller venous flow velocity of 1.25 cm/min was chosen. It should be noted, however, that the venous flow velocity should not have any effect on the results of the experiments. The experimental set up is designed to record changes in infusion line pressure. The volumetric flow rate in the venous line should have no bearing on the infusion line pressure. Only the venous line pressure, which exerts a back pressure on the inserted cannula and so on the infusion line flow, will have any effect on the experimental results.

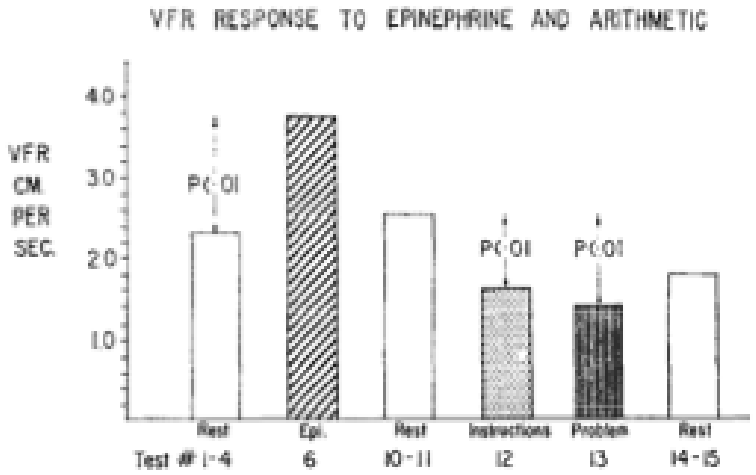

Figure 18: The experimental venous flow velocities in adult women with medication-induced variations (Silverman and McGought 1971)

8.2.3 Tubing

The type of tubing used was silicone rubber tubing as it allows for penetration of the infusion cannula without causing catastrophic failure of the line, nor causing a discernable effect on the flow and pressure within the venous circuit. The tubing size was chosen as the smallest available, to best mimic the size of a large vein into which and infusion site might be made in a clinical setting. The venous tubing at the level of

insertion had an internal diameter of 2.4 mm with a wall thickness of 1.6mm. At the level of the peristaltic pump it was necessary to increase the size of the silicon tubing to fit the peristaltic pump without backflow.

8.2.4 Pump

Figure 19: Watson-Marlow 101 UR roller pump (Watson-Marlow Pumps 2006)

The pump used to power the venous circuit was a Watson-Marlow 101U/R roller pump, shown in figure 18. The peristaltic pump is variable speed with roller speeds between 2 and 32 rpm. The pump speed is changed manually and is denoted by a unitless numerical value between 0 and 99. The pump head is manually loaded with silicone rubber tubing (Watson-Marlow Pumps 2006).

8.2.4.1 Pump Calibration

The pump speed being denoted by a unitless value between 0 and 99, pump speed determination and calibration was required to determine the speed profile of the pump and to determine the correct setting for venous circuit use.

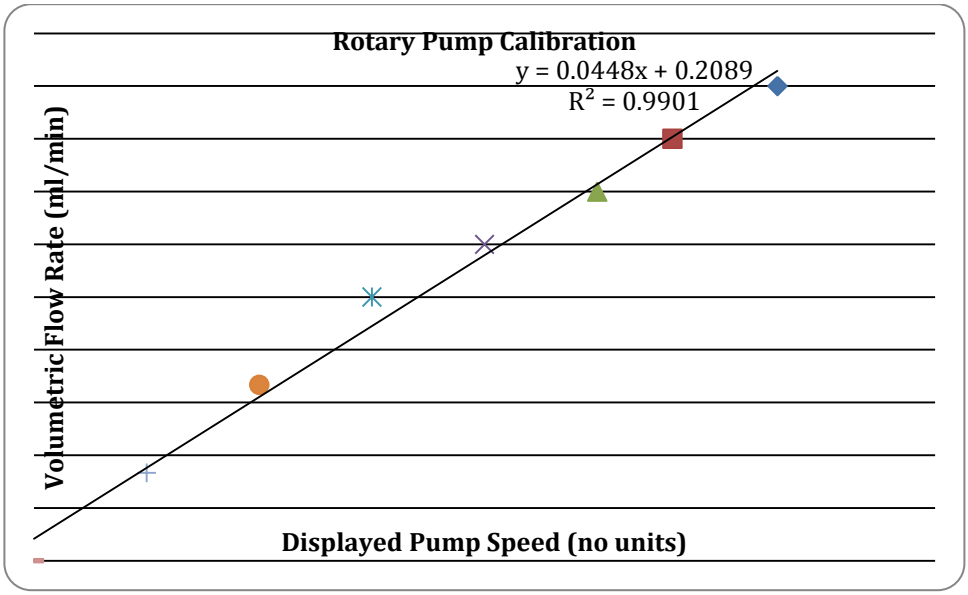

Figure 20: Calibration of Watson Marlow pump speeds

The pump calibration curve, shown in figure 20, was composed by running the pump at 8 different speeds for a duration of three minutes at each speed. The pump output was collected in a clean, empty graduated cylinder. The total pump discharge collected, in ml, was divided by the three minute duration to obtain a debit in ml/min. Considering that the speed/flow rate relationship of the pump was determined in ml/min and the desired venous flow velocity was given in cm/min, it was required to find the appropriate conversion for the silicone rubber tubing in question.

$$A = \pi r^2$$

$$A = \pi\ 1.2^2 = 4.52\text{mm}^2$$

$$Flow\ rate = \frac{\boldsymbol{1.2}5cm}{min}$$

$$1cm^3 = 1mL$$

$$volumetric\ flow\ rate = flow\ velocity * area$$

$$Volumetric\ flow\ rate = \boldsymbol{1.25}\frac{cm}{min} * 60s/min * 0.045\ cm^2 = 3.39\frac{ml}{s}$$

From the equations above, it can be seen that the pump was chosen to run at a nominal speed of 75 to achieve a flow rate of approximately 3.5ml/min. This flow rate was verified using a graduated cylinder and a stopwatch prior to experimentation.

8.3 Infusion Circuit

8.3.1 Set Up

The infusion circuit was set up in the same manner as in infusion pump would be set up and readied to use in a clinical situation, a schematic. The main difference between the laboratory set up and that in a clinical setting was the location of the infusion pump with respect to the infusion site. In a clinical setting the infusion pump is mounted on a pole near to patient. This often results in a height differential between the pump and the patient. Furthermore the length of infusion line between the pump and the catheter is variable and likely to be longer in a clinical setting than was set up in the laboratory. A pressure sensor was added into the infusion line at the position shown in figure 21.

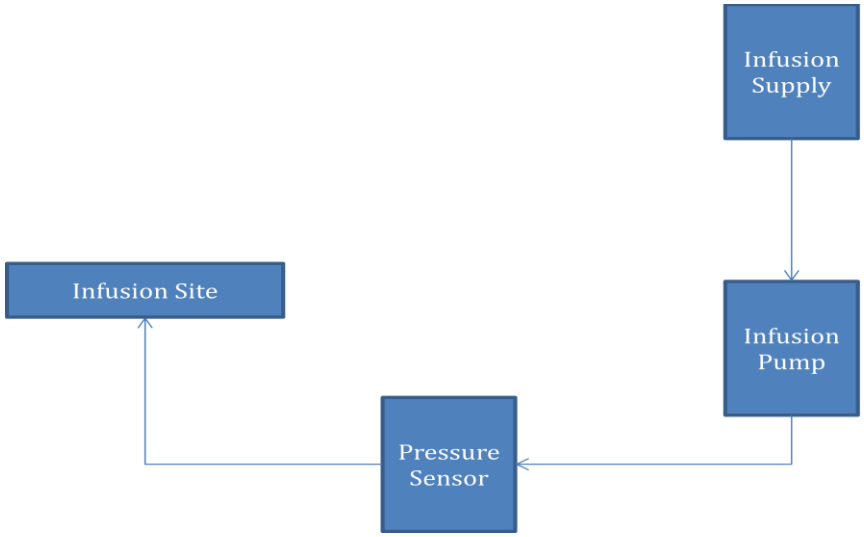

Figure 21: Schematic of the infusion circuit

Neither of these discrepancies should affect the validity of the experimental results. The height deferential between the pump and the infusion site would result in a higher line pressure at the site of infusion due to the fluid pressure head associated with

the difference in height. However this pressure head would be constant and would not affect the detection of the pressure changes that would indicate infiltration or extravasation had occurred. The longer infusion line would create a similar, constant, increase in line pressure due to resistance in the line. This would not affect the detection of extravasation for similar reasons.

8.3.2 Flow Parameters

The infusion circuit was run at several different flow rates. The variation in flow rates from 10 ml/h to 75 ml/h was used to ensure that the experimental results were valid across all flow rates and that the detection of infiltration could be done independent of pump flow rate. The maximum flow rate of 75ml/h was chosen due to the stutter that the syringe pump acquired at higher flow rates. At high flow rates, a syringe pump will often exhibit a stuttering flow characterised by small, rhythmic fluctuations in the inline pressure.

8.3.3 Tubing

The tubing used to connect the syringe pump to the catheter was of the same type as that used in the infusion circuit, namely medical grade silicon tubing with an internal diameter of 2.4mm and a wall thickness of 1.6mm. This was attached by luer lock to the pump's syringe at one end and to the catheter line at the other.

8.3.4 Infusion Pump

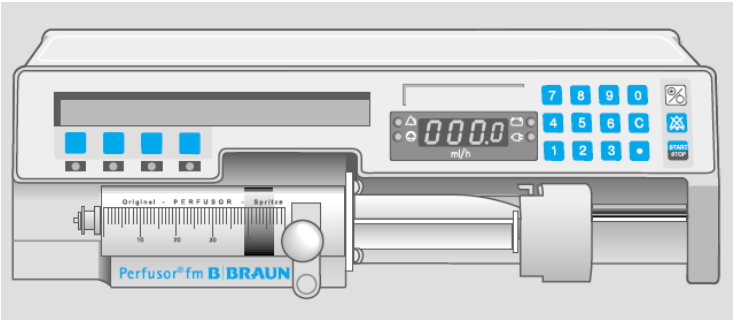

Figure 22: Braun Perfusor fm pump (Braun Hospital Care 2001)

The infusion pump used was a Braun Perfusor syringe pump, shown in figure 22. A syringe pump was used because of the wide range of applications for syringe pumps and their high accuracy. Syringe pumps are used in both adult and paediatric applications. When used for adults, the syringe pump is typically used at lower flow rates than a volumetric pump (Braun Hospital Care 2001). Syringe pumps are often used in paediatric applications where accuracy is highly important and lower flow rates are common due to lower body mass. As the venous circuit was set up to resemble that of a child it is consistent with this presumption to use a syringe pump in the infusion circuit.

8.4 Pressure Sensors and Software

8.4.1 Data Acquisition

A BioPac Systems Inc. data acquisition software system was used to monitor and record the inline pressures in both the venous and the infusion circuits during experimentation (BioPac Systems Inc 2012). The BioPac AcqKnowledge system was connected to two blood pressure transducers, shown in figure 23, designed to measure blood flow in animals, and therefore having an operation range suitable for this application. The pressure transducers, connected in line in the experimental circuits, fed pressure data back to the BioPac system, which was than displayed on screen and recorded. The data was then saved in Excel files to facilitate analysis.

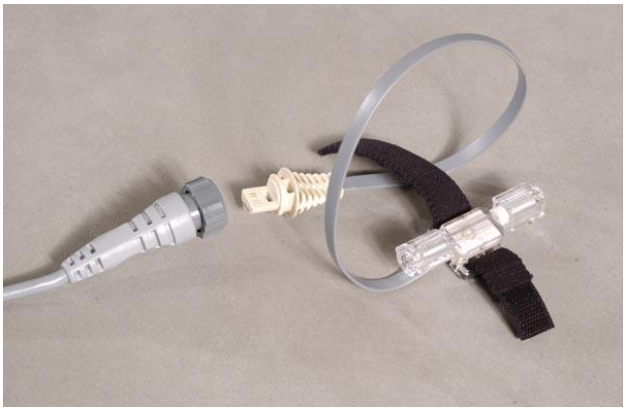

Figure 23: BioPac blood pressure transducers (BioPac Systems Inc 2012)

8.4.2 Zero Drift

The blood pressure transducers are very sensitive and picked up noise from the surrounding laboratory equipment. This noise would cause a zero drift in the transducer outputs, so that when the sensors were not under any pressure loading they would read a small positive pressure rather than zero. To compensate for this zero drift the sensors were connected to the BioPac system and readings taken prior to the connection of the infusion and venous circuits. The recorded pressure was taken as the zero drift and this amount was subtracted from all of the recorded pressures during experimentation to correct for the drift. The zero drift of the sensors was within 3 to 8 mmHg. The zero drift of the pump during each trial is shown below in table 4. Note that two data sets at a 10ml/h flow rate are present because two separate trials were run at this speed. The first trail run at this speed was identical to those run at high infusion rates. The second trails at 10ml/h was run to provide a view of multiple, rapid insertions and removals of the cannula into the insertion site. The results of this trial can be seen in figure 31.

Table 4: Zero-drift values of pressure sensors during experimental trials

Zero-Drift of Experimental Pressure Sensors		
Flow Rate (ml/h)	**Zero Pressure Reading (mmHg)**	
	Venous Sensor	Infusion Sensor
10	8	4
10	7	4
25	6	3
50	7	3
75	6	5

8.5 Infusion Site

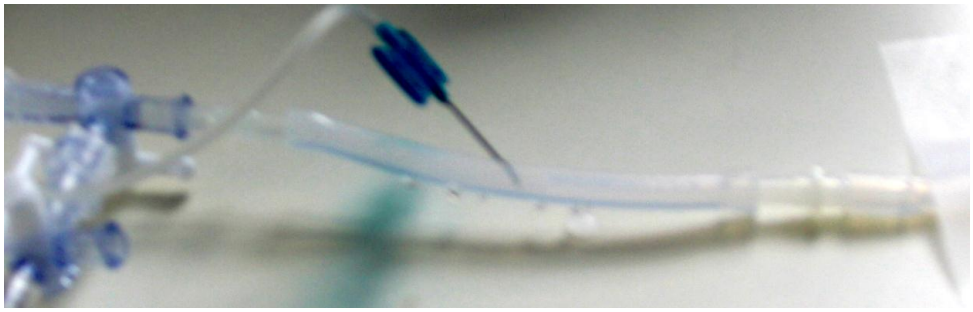

Figure 24: Infusion site in venous circuit

The infusion site in the venous circuit, which can be seen in figure 24, for experimentation was set up as a separate length of silicone rubber tubing, 2.4mm internal diameter and 1.6mm wall thickness, connected via press fit connectors to the main line, and an 18 gauge cannula was used to infuse into the venous circuit. The infusion site was set up as a separate piece of tubing so that it could be easily replaced without replacing the entire circuit. The infusion site tubing was replaced prior to each set of experiments to ensure that the punctures in the infusion site from the previous trials did not affect the integrity of the line or the validity of the results for the next cycle of testing.

9. Experimental Procedure

The experimental procedure described was followed for each trial to ensure reliable, representative and repeatable results that could be used to draw conclusions about the possibility of detecting extravasation of infusion lines through the monitoring of inline pressure in the infusion line near the insertion site.

To prove that extravasation could be detected using inline pressure monitoring of the infusion line, the outlined experimental design was set up. The two circuits were set up as described and the pressure sensors and associated software were turned on to get a baseline reading of the pressure in each line.

9.1 Venous Circuit Set Up

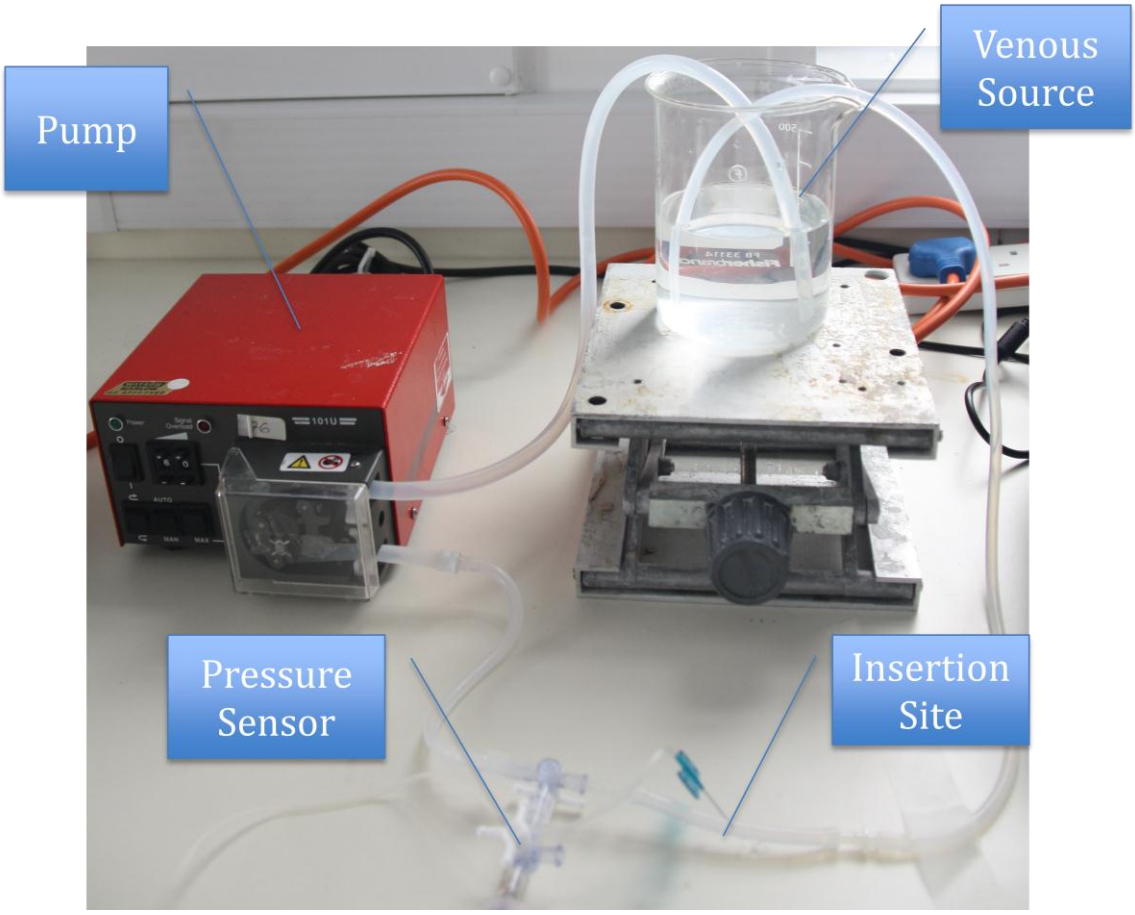

Figure 25: Picture of Venous Circuit

Once the venous circuit was set up as can be seen in figure 25, the silicone rubber line at the infusion site in the venous circuit was replaced with a new section of tubing. The venous line was then primed with saline solution and the pressure sensor monitoring the infusion line was primed and wired into the pressure monitoring software. This allowed for a baseline zero drift of the pressure sensor to be read to ensure an accurate reading. The zero drift in the pressure sensor could be due to a number of factors, such as noise in the system, and gave a consistent reading of approximately 5-8 mmHg. This zero drift was recorded at the beginning of each session and was subsequently subtracted from the absolute pressure values during data analysis.

Once the venous line was primed and the pressure sensor zero drift recorded the venous pump was turned on and the change in pressure recorded. The height of the venous line source was then adjusted to achieve a venous line pressure of 10 - 12mmHg. Once this was achieved, the venous line source was secured at the correct height and the infusion site and venous line pressure sensor were secured in place on a flat, horizontal surface to minimize artefact error associated with movement of the insertion site or of the pressure sensor.

9.2 Infusion Circuit Set Up

The infusion circuit was set up as shown in figure 26. Prior to the insertion of the catheter into the infusion site in the venous circuit, the infusion circuit was checked for leaks and the infusion source was filled to capacity. When the Perfusor syringe pump was used a 60ml syringe was filled with saline solution and the infusion line primed with the same. When this was done, the infusion line pressure sensor was wired into the pressure monitoring program to read the zero drift of the infusion line pressure sensor. The zero drift was recorded to be subsequently subtracted from the absolute pressure reading during data analysis.

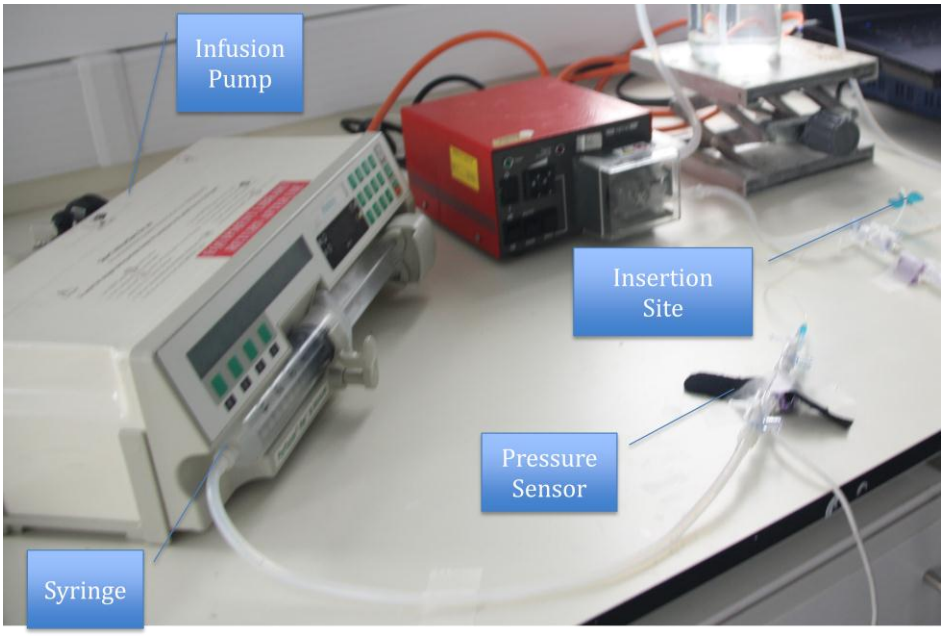

Figure 26: Picture of infusion circuit

The pump was turned on and the occlusion alarm set to high so as not to alarm easily. The desired infusion rate was chosen and the infusion started. The flow was then checked as the infusion pump was allowed to run for two minutes into an empty receptacle. This ensured proper pump functioning and that all air bubbles were clear of the line prior to infusion. Once the proper functioning of the infusion pump, line and pressure sensor were assured and the zero drift recorded, the catheter was inserted into the infusion site in the venous circuit.

9.3 Experimental Trials and Data Recording

After setting up both the venous and infusion circuits and recording the baseline pressures in each, the catheter of the infusion line was inserted into the venous circuit at the infusion site. The pressure monitoring software started recording. The pressure readings were allowed to come to equilibrium and the catheter was removed after twenty seconds had elapsed. The catheter was reinserted ten seconds later at the thirty-second mark to allow the new pressure readings to come to equilibrium prior to reinsertion. This was repeated every ten seconds for a total of ten removals and insertions. At the completion of ten cycles the pressure monitoring software stopped recording and the infusion pump was shut off. The venous pump was allowed to continue running throughout the experimental trials.

9.3.1 Data Recording

Once a single trial of ten cycles had been completed and the infusion pump switched off the data generated was recorded. The entire set of data including time and pressure readings from both sensors was first recorded in its entirety. Then, after recording the baseline pressures, zero drifts and any interesting aberrations in pressure data or errors in experimental procedure that might have affected the data, the data was subdivided and exported to Microsoft Excel for analysis. A separate Excel file was created with the data from each removal of the catheter from the venous circuit, along with the equilibrium values to either side of the area of interest. This allowed for the

analysis of pressure changes during infiltration. Each Excel file noted the trial and cycle number and the infusion rate during each trial. These were saved for further analysis.

9.3.2 Experimental Trials

The experimental procedure described was repeated for several trials at various pump speeds to prove that the infusion line pressure changes associated with the detection of infiltration were able to be detected independently of infusion rate. The Perfusor syringe pump, typically used at lower infusion rates, was tested at 10ml/h, 25 ml/h, 50ml/h and 75ml/h flow rates (Braun Hospital Care 2001).

For each trial the venous pressure was set to low but physiologically acceptable levels of around 10 mmHg. The low venous pressures were chosen because lower venous pressures would cause smaller pressure changes and be more difficult to detect accurately. If the small pressure drops associated with low venous pressures can be accurately detected during infiltration then larger pressure drops associated with higher venous pressures should be easily detected as well.

The inline infusion and venous pressures were continually sampled throughout the testing procedure at a rate of 1000Hz. This was chosen so as to be able to detect the smallest and quickest of pressure changes. The experimental procedure for each trial was performed in the manner described and the data recorded in the same manner.

10. Experimental Results

The theory that inline pressure monitoring could detect infiltration through a loss in pressure associated with the fluid flow pressure in the venous system into which the infusion takes place was tested using the experimental procedure outlined above. It was shown that the removal of the catheter needle from the venous circuit, representing the infiltration of a needle from the vein into which it was inserted, was characterised by a drop in inline pressure in the infusion line. The pressure in the venous line showed no discernable changes. The pressure drops in the infusion line were easily detected by the inline pressure sensor used in the experimental set up.

10.1 Trial Results

A total of forty trials at four different infusion rates were conducted and recorded. The pressure drop associated with infiltration, modelled by pulling the cannula out of the venous circuit, was taken by calculating the difference between the average pressure just prior to infiltration and the average pressure after the inline pressure had stabilised at a lower value. The time elapsed between the first sign of a pressure drop and the stabilisation at a lower pressure was also measured and recorded. The pressure drop and associated time for each trial is shown in table 5.

Table 5: Pressure drops and associated times for all trials

Pressure Drops During Infiltration			
Flow Rate	**Cycle**	**Pressure drop (mmHg)**	**Time (s)**
10 ml/h	1	10.08	1.39
	2	11.17	1.20
	3	10.31	1.48
	4	9.67	0.84
	5	9.90	1.27
	6	12.78	1.96
	7		
	8	11.01	1.79
	9	10.75	0.93
	10	10.24	0.90
	Avg	**10.66**	**1.31**
25ml/h	1	7.65	1.40
	2	12.44	1.88
	3	11.96	1.79
	4	13.33	2.02
	5	13.89	2.12
	6	14.33	2.22
	7	12.57	1.35
	8	11.50	1.27
	9	9.19	1.21
	10	13.67	2.02
	Avg	**12.05**	**1.73**
50ml/h	1	8.34	1.24
	2	9.75	1.20
	3	10.31	1.48
	4	9.88	1.12
	5	8.36	0.81
	6	8.97	0.77
	7	10.64	1.12
	8	10.07	0.88
	9	8.98	0.95
	10	12.16	2.10
	Avg	**9.75**	**1.17**
75ml/h	1	5.37	1.89
	2	6.73	0.48
	3	9.53	1.13
	4	12.85	1.15
	5	10.91	1.15
	6	12.54	1.08
	7	12.49	1.37
	8	12.49	1.32
	9	9.73	0.84
	10	10.00	1.00
	Avg	**10.26**	**1.14**

There is no data from cycle 7 at a 10ml/h infusion rate as there was signal interference happening at this time. It is unknown what caused the interference but the values obtained showed negative pressure in the infusion line. This was not possible due to the pressure exerted by the infusion pump and the positive height displacement between the infusion pump and the insertion site. It was determined that these results was an aberration caused either by noise, jostling of the pressure sensor and its connections or some other outside source. Consequently this measurement was considered null and was not included in the data set.

The inline infusion and venous pressures were plotted against time during the period of infiltration. The most characteristic graphs for each infusion rate are shown in figures 27 through 30.

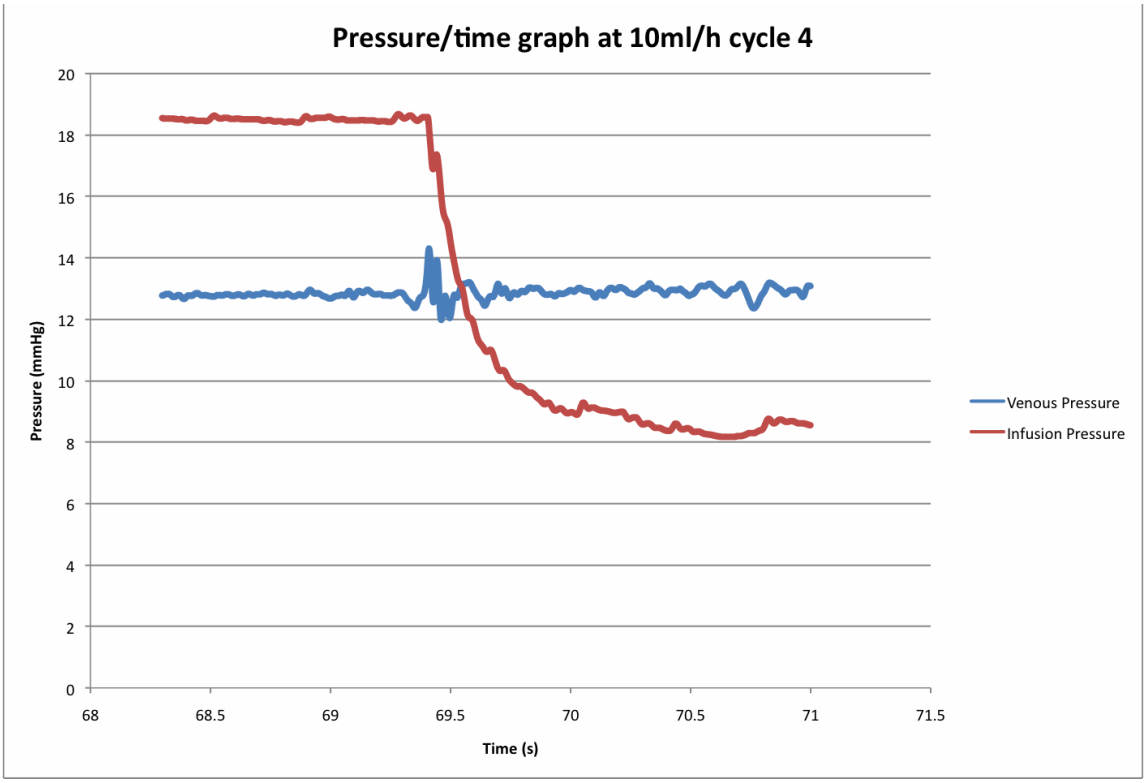

Figure 27: Infiltration induced pressure drop at 10mL/h infusion rate

The data for the cleanest trial recorded at an infusion rate of 10mL/h is shown in figure 27. The pressure drop curve at low infusion rates is the smoothest of the pressure drop curves. This could be due to a number of factors. Syringe pumps have a tendency to show signs of a stutter at higher infusion rates, which is reflected in the inline pressure. At lower infusion rates pressure does not build up as quickly in a line when a temporary obstruction occurs, as there is less fluid flowing down line during the obstruction period.

Note that the rapid change in venous line pressure occurring at 69.5 seconds in figure 27 is a periodic occurrence inherent to the operation of the venous line drive pump. The small changes in venous pressure do not affect the inline pressure readings in the infusion line.

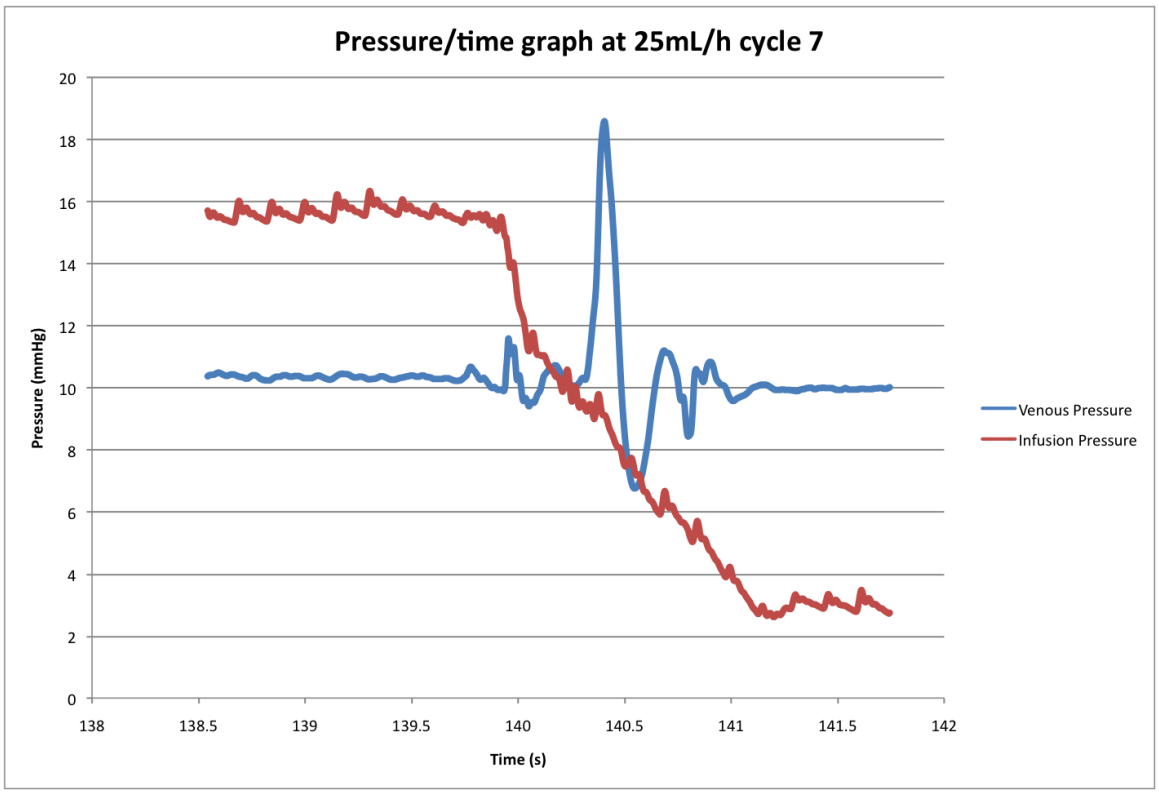

Figure 28: Infiltration induced pressure drop at 25ml/h infusion rate

Note that the periodic rise and fall in the infusion line pressure in figure 28 as a result of the stutter in the syringe pump is more pronounced than at the 10 mL/h infusion rate in figure 27. The stutter does not, however, affect the overall trend of the pressure drop, which is clearly distinguishable.

The large, rapid changes to the venous line pressure seen in figure 28 were due to temporary obstruction of the venous line as the infusion cannula was pulled out of the venous line. This was noted at the time of experimentation but was not corrected, as obstruction of the venous line during infiltration is a plausible scenario in an *in vivo* situation. The large pressure changes in the venous line appeared to have a slight effect on the infusion line pressure. The slope of the infusion line pressure drop appears to flatten out slightly at the same time as the high-pressure occurrence in the venous line. Note that this does not inhibit the clear presentation of the characteristic pressure drop in the infusion line, nor does it noticeably increase the time it take for the pressure drop to manifest.

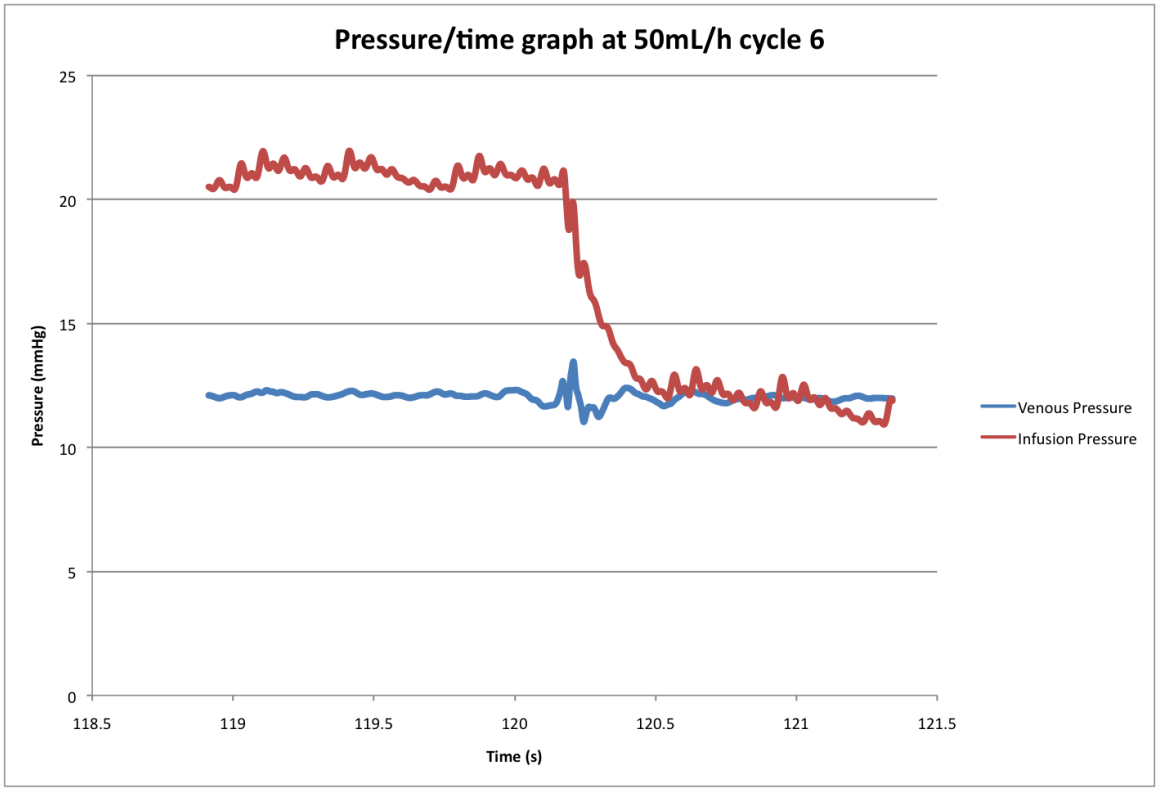

Figure 29: Infiltration induced pressure drop at 50 ml/h infusion rate

Note the more evident periodic pressure changes in the infusion line due to the syringe pump stutter seen in figure 29, depicting a trial at an infusion rate of 50ml/h. Though the stutter-induced changes grow more pronounced, they still do not inhibit the ability to discern the characteristic pressure drop associated with infiltration.

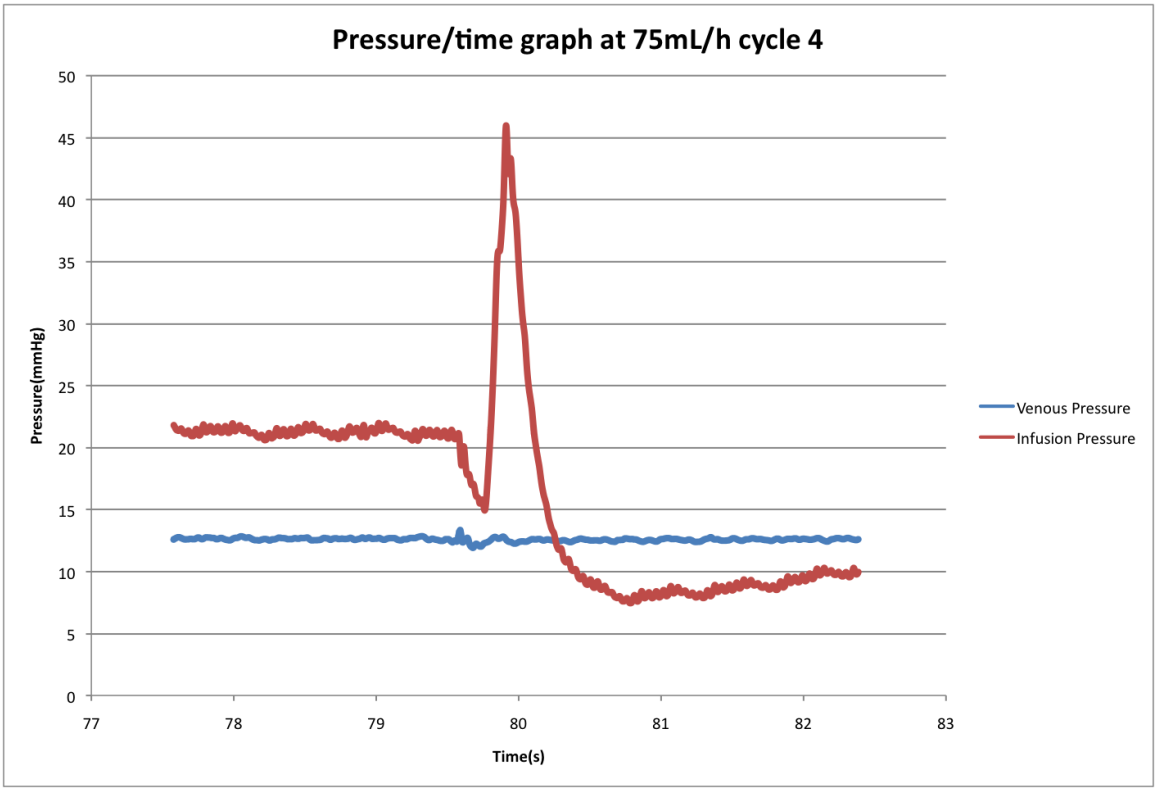

Figure 30: Infiltration induced pressure drop at 75 ml/h infusion rate

The pressure graph showing infiltration induced pressure changes at an infusion rate of 75mL/h, figure 30, is the only graph to differ significantly from those taken at lower infusion rates. During all ten cycles of infiltration at the highest infusion rate there occurred a rapid upswing in infusion line pressure directly preceding the drop characteristic of infiltration. This upswing is a result of the wall thickness of the silicone tubing making up the infusion site. Unlike natural veins, where the ratio of wall thickness to internal diameter is relatively low, the corresponding ratio for the silicone tubing used is very high. This was unavoidable and a consequence of the types of tubing available during experimentation. At low flow rates the wall thickness had no discernable effect on the experimental results. However at the highest flow rate of

75mL/h the effect was clearly seen. Due to the relatively rapid flow of fluid through the infusion line at the highest infusion rate, the obstruction provided as the cannula passed though the wall of the silicon tube during infiltration caused a pressure build up in the infusion line. This pressure build up caused an increase in inline pressure and was recorded by the pressure sensor in the infusion line. The pressure build up was immediately released when the cannula cleared the wall of the silicone tubing and thereafter can be seen the characteristic pressure drop induced by infiltration. It is unlikely that this upswing in inline pressure would be seen in an *in vivo* situation as the wall of the vein are much thinner than those of the silicon tubing and no discernable pressure increased is known to be associated with infiltration.

The characteristic curve of infiltration induced pressure drops in the infusion line can be seen more clearly when a series of pressure drops are observed. To demonstrate the characteristic curve fully a series of measurements were taken at an infusion rate of 10mL/h with the cannula withdrawn from the venous circuit and reintroduced in two-second intervals and the results displayed in figure 30. The data was sampled at a rate of 1000Hz but was reduced to a sampling frequency of 4 Hz so that a graph over a longer time scale could be made. The detail lost in the lowering of the sampling frequency was not considered relevant as this detail was retained in the graphs of individual infiltration trials. The only discernable effect of the lower sampling rate was the smoothing out of the infusion line pressures when at equilibrium as the small cyclic fluctuations were less visible.

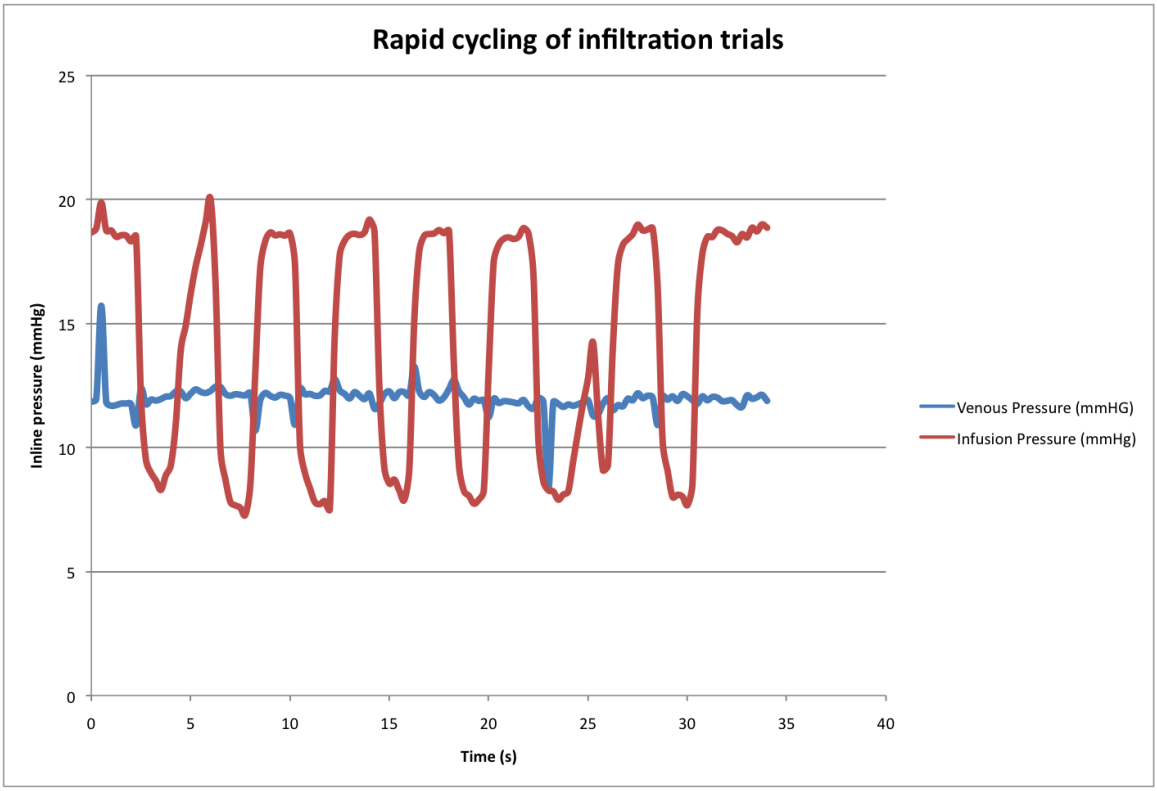

Figure 31: Demonstration of characteristic curve of infiltration-induced pressure drops

In figure 31, depicting rapid removal and reintroduction of the cannula into the insertion site, some operator errors may be seen in the second and seventh attempts to reintroduce the cannula into the venous circuit. The characteristics of the infiltration-induced pressure drop are still visible. The pressure drop is close in magnitude to the average venous pressure, in this case between 9 and 12 mmHg in magnitude when the average venous pressure was 12.05 mmHg. The pressure drop starts very abruptly at the removal of the cannula and falls precipitously with a steady slope. The slope of the pressure drop rounds off slightly prior to the lowest pressure recorded. Please note that the slight dip in pressure directly preceding the rise associated with the insertion of the cannula is likely due to the movement of the cannula required for insertion and should not be taken as part of the characteristic curve of infiltration-induced pressure drop.

10.2 Venous Pressure Drops

The pressure drops across the 40 cycles were relatively consistent, as were the time periods associated with the pressure drops. The pressure drops associated with the infiltration trials were then compared to the average venous circuit pressures to confirm the hypothesis that the pressure drops characteristic of infiltration would be approximately equal to the venous pressure.

Table 6: Average experimental venous pressures

Venous Pressures (mmHg)				
Cycle	**Flow Rate (ml/h)**			
	10	25	50	75
1	12.00	9.97	11.83	12.10
2	12.01	10.00	11.71	12.21
3	12.03	10.55	12.40	12.31
4	11.86	10.96	12.18	12.56
5	11.96	10.37	13.22	13.08
6	12.04	10.36	12.06	13.43
7	-	10.30	12.09	13.59
8	12.20	10.25	12.14	13.71
9	12.21	10.94	12.20	13.92
10	12.17	11.18	12.16	14.05
Average	**12.05**	**10.49**	**12.20**	**13.10**

The pressure drops caused by the removal of the cannula from the venous circuit, mimicking infiltration, are similar in magnitude to the fluid pressure in the venous circuit and can be seen in table 6. This is as expected and shows that infiltration of an infusion line produces a predictable pressure drop over a predictable time period that could be used a an early detection method.

11. Significance of Experimental Findings

In accordance with the findings of Guy and Pons de Vincent (1992) (Guy and Pons de Vincent 1992), the monitoring of inline pressure in an infusion line could be used to detect the early signs of infiltration, extravasation and possibly line disengagement by detecting the characteristic pressure drop associated with these events. By proving that inline pressure monitoring can lead to early detection of these problems it becomes possible to design an engineering solution to the problem of endangered patient safety due to infusion line decoupling and infiltration in a clinical setting. The simplest and most expedient design for an early detection of infiltration and line decoupling in infusion lines would be a highly sensitive inline pressure sensor incorporated into a luer lock connector.

It should be noted that to truly mimic infiltration in an experimental setting a medium mimicking the subcutaneous tissue should have surrounded the infusion site. The cannula would then have been removed from the venous circuit and infused into the experimental subcutaneous tissue. However, it has been shown that the backpressure asserted on the infusion line by the subcutaneous tissue is negligible in the time frame relevant to the experimentation performed in the lab. The increase in pressure due to the swelling of the subcutaneous tissue takes time to rise to non-negligible levels (Rose, et al. 2008). Thus the results of the current set up can be applied to the event of infiltration despite the lack of subcutaneous tissue modelling.

11.1 Potential Benefits

This solution has the benefits of simplicity and ease of use. The design would require no further training, as luer locks are already the line connection of choice in clinical settings. The small size of the final product would not create unnecessary clutter at the patient bedside. The luer lock design also has the advantage of being easy to incorporate into the design and operation of an infusion pump, allowing monitoring software and alarm capacities to be incorporated into the circuitry of the infusion pump

and take advantages of the existing alarm features. This would ease the clinical adoption of the product and could provide a tangible benefit to a new generation of infusion technologies.

11.2 Working Parameters

A successful inline pressure sensor-based solution for the early detection of infiltration and line decoupling would be required to operate within the working parameters of all possible infusion scenarios. Typical parameters are shown below.

- Pressure range from 0 to 200 mmHg (MHRA 2010)
- Flow rates from 0 to 9999ml/h (Braun Hospital Care 2001)
- Variable viscosity fluids (MHRA 2010)
- Temperature range from 15-40°C

11.3 Existing Technology

The German company SensorTechnics produce medically approved pressure sensors that meet the ISO 13485:2003 standard and can be made to custom design specifications (SensorTechnics 2010) (see Appendix B for full range). The HMA series amplified pressure sensor would be a good fit for the required working parameters (SensorTechnics 2012). The technology exists to create the proposed luer lock based design.

11.4 Detection of Infiltration and Line Disengagement

The detection of infiltration and line decoupling can be done as the experimental results show that infiltration produces a definite and precipitous pressure drop approximately equal in magnitude to the venous pressure of the patient. This has also been proven in 1992 by Guy and Pons de Vincent and by Harris and von Maltzahn in 1993 (Guy and Pons de Vincent 1992) (Harris and von Maltzahn 1993). The detection of infiltration and line disengagement could then be done using a software program to compare the pressure monitoring data to mathematical models of normal infusions,

infiltrations and decoupled lines. Models could be expanded to include benign deviations to normal infusion behaviour such as temporary kinks in the line and patient movement artefacts. A third order system model was developed by Harris and von Maltzahn in 1993 and was successfully used to differentiate infiltration behaviour from normal infusion behaviour and various benign variations shown in figure 31 (Harris and von Maltzahn 1993).

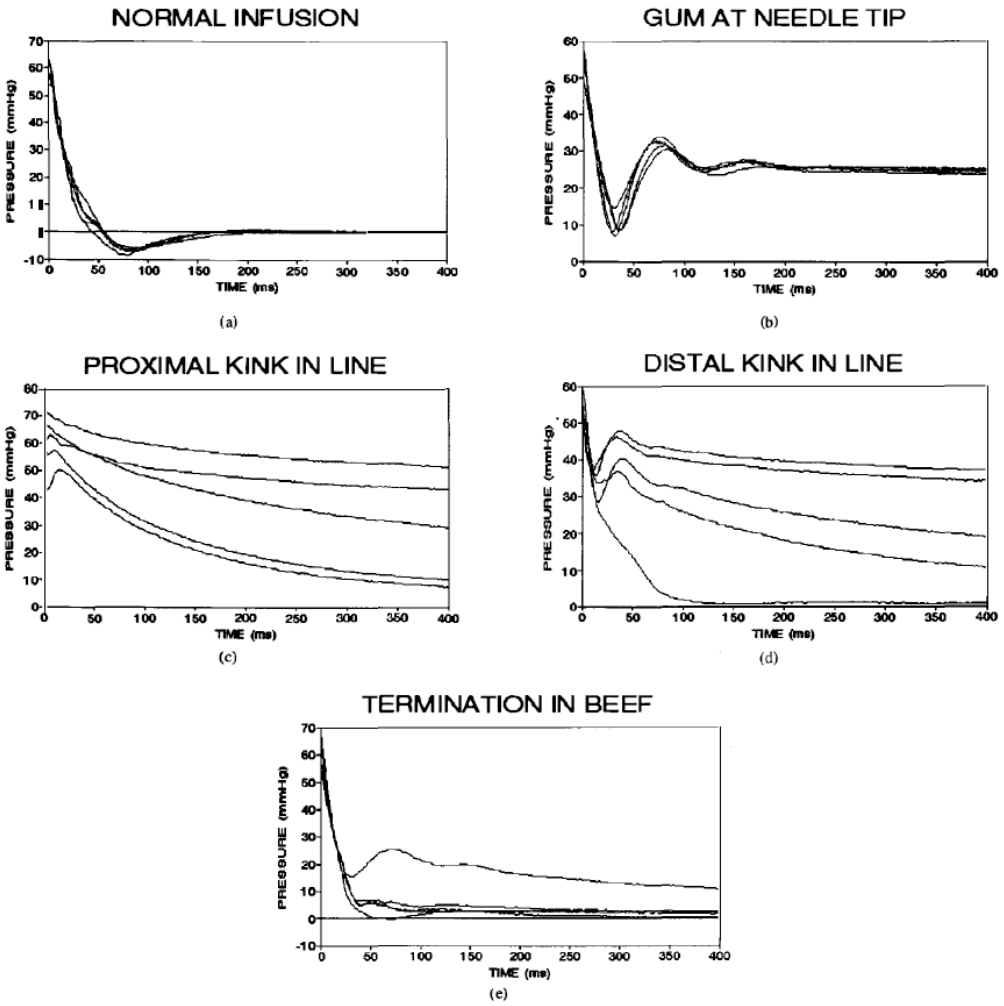

Fig. 3. (a)–(c) Experimental curves of five new IV-lines under various termination conditions

Figure 32: Experimental behaviour of inline infusion pressure (Harris and von Maltzahn 1993)

A third order system was found to model all five behaviours and described the model using the differential equation (Harris and von Maltzahn 1993):

$$\frac{d^3p}{dt^3} + a\frac{d^2p}{dt^2} + b\frac{dp}{dt} + cp = 0$$

A similar model could be used to detect infiltration and line decoupling from the pressure data generated from the luer lock based pressure sensor design.

The luer lock design would also require an alarm component so as to alert nursing staff when infiltration or line decoupling had been detected. Should the design hold up well in clinical trials, the adoption of inline pressure sensors to monitor infiltration by infusion pump manufacturers would allow for the integration of the detection models and software with the existing software in the infusion pump. The alarm required to alert staff to infiltration or line decoupling could than use the existing occlusion alarm systems in place. This would require little effort on the part of the manufacturer and would not need to add to the size of the infusion pump.

12. Future Directions for Clinical Application

The basic theory of using inline pressure monitoring to detect infiltration and line decoupling has been proven both here and in previous research (Guy and Pons de Vincent 1992) (Harris and von Maltzahn 1993). However there is yet to be a product on the market that uses this theory to detect infiltration. Various patents have been filed using some form of pressure monitoring or pressure response to detect infiltration, yet none have been adopted into clinical practice or been manufactured on a commercial scale (Kamen 1989) (Burkett 1995). There are several steps that must be taken prior to commercialisation to improve the chances of clinical adoption.

12.1 Working Prototype

To further research in the suitability of a luer lock based inline pressure monitoring system a working prototype must first be developed. Further testing should be done on a prototype closely resembling the final product to ensure maximum relevancy of the results and to push towards commercialisation.

12.1.1 Testing of Prototype

Once the prototype has been established testing should be done both *in vitro* and *in vivo* in animal studies. *In vivo* studies will show that the characteristics of infiltration found in *in vitro* testing hold true when studied in vivo and that the surrounding tissues, the differences between physiological conditions and those replicated in the laboratory, movement artefact, and any number of variations between *in vivo* and simulated situations do not affect the ability to detect infiltration by monitoring inline pressure.

12.2 Infusion Behaviour Model

To allow for automated detection of infiltration from inline pressure data a mathematical model of infusion behaviour must be produced and tested. The model could be used to characterise the different pressure patterns found in various infusion behaviours, as was done by Harris and von Maltzahn (Harris and von Maltzahn 1993).

Their model was based on a third order system and accurately parameterised the experimental pressure behaviour recorded during infiltration, among other scenarios. A model must be created that is highly accurate in characterising infusion line pressure behaviour and that can detect infiltration with a high degree of accuracy and a low occurrence of false alarms.

The model would than require testing to prove the accuracy of the results and the ability to detect infiltration with a low and acceptable number of errors. The testing of the model could occur in conjunction with the testing of the working prototype, and should be done both *in vitro* and *in vivo* to ensure maximum accuracy and minimal potential errors.

12.3 Adoption by Infusion Pumps Manufacturers

Should the model and prototype be proven successful, clinical trials would proceed. Once the technology is proven to the satisfaction of the medical regulations community, clinical success would be most likely if the technology was adopted by infusion pump manufacturers and incorporated into the design of the next generation of infusion pumps. This would negate the requirement for a separate and new piece of technology to be adopted by clinicians and would allow for the integration of the electrical, software and alarm requirements to use existing systems in the infusion pump. This would ensure the ultimate success of infiltration detection by inline pressure monitoring technology.

13. Final Remarks

It appears that the idea of inline pressure monitoring being used for infiltration detection is not a new one. It received attention in the late 1980s and early 1990s, as evidenced by several papers proving the efficacy of the technology and the submission of several patents for devices using this theory to monitor infusion lines (Guy and Pons de Vincent 1992) (Harris and von Maltzahn 1993) (Kamen 1989) (Burkett 1995). However there is no indication that either the studies or the patents were followed up or underwent the clinical trials required for commercialisation. This begs the question as to what inhibited the progress of this technology at that time. It is hypothesised that either a lack of funding or an inability to manufacture small, accurate, disposable pressure sensors for a sufficiently low cost was a contributing factor.

It should be noted that there has been marked advancement in pressure sensing technologies and in the pressure sensor market since the late 1980s and early 1990s. It is likely that the technology required to produce accurate pressure sensors with robust design on a commercial scale, at a cost conducive to disposable products, did not exist at the time that previous research was being done in this area. However, the market for pressure sensors has moved on considerably in the last 25 years, therefore this should no longer be a drawback in the adoption of this technology. The reasons behind the failure to capitalise on the study of inline pressure monitoring done in the early 1990s bears further investigation as further considerations for commercialisation and clinical adoption may be raised in the course of this investigation.

The adoption of this technology by infusion pump manufacturers would ensure the resources and manufacturing ability required were available, as well as increasing the likelihood of commercial success and clinical adoption. This would be most easily achieved by a partnership between academia and industry in the development and testing of prototypes and models to detect infiltration through inline pressure changes. Success in clinical adoption could lead to a substantial decrease in the incidence of infiltration

and extravasation injuries as well as negative side effects related to line decoupling and subsequent under dosage of medication.

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Appendix A: Initial Problem Definition

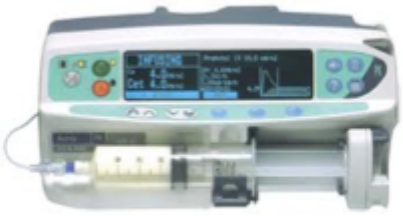
"PATIENT SAFETY DESIGN"

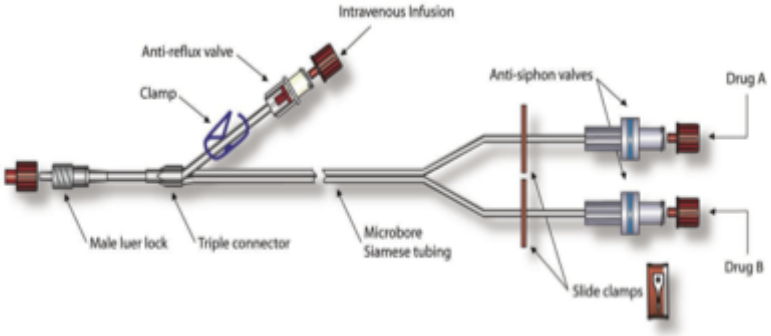
T Vassalos

BACKGROUND

External infusion pumps are medical devices that deliver fluids, nutrients and medications (including anaesthetics, chemotherapy, insulin, antibiotics, adrenaline, morphine and other pain killers) into a patient's body in a controlled manner. They are used extensively in all hospital areas as well as in the community. A trained user normally operates the pump by programming the rate and duration of fluid therapy through the built in software.

The infusion pump is usually connected to a patient's drip via a standard luer lock mechanism using a specific administration set that includes anti-siphon and anti-reflux valves to reduce the risk of free-flow and back-flow respectively. [1]





Fifteen million infusions are performed in the NHS alone each year with an average of over 1000 pumps available per trust. The vast majority of infusions are delivered safely, however at least 700 unsafe incidents are reported to the UK National Patient Safety Agency every year of which 5.2 to 21% are attributed to underdosage (including apparatus disconnection) with some fatal or serious harm outcomes (including awareness during anaesthesia). [2-5]

PROBLEM

Although infusion pumps have many safety features including several alarms (air entrainment, line occlusion, power failure, end of infusion and equipment misloading) they do not currently detect or prevent patient disconnection.

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Appendix B: SensorTechnic HMA Series Specifications

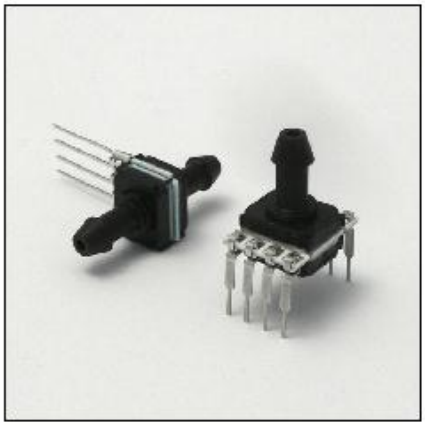
HMA Series
Amplified pressure sensors

This data sheet describes preliminary development samples to be used only for the development process.

PRELIMINARY

FEATURES

- 100 mbar to 10 bar, 1 to 150 psi gage or differential pressure
- Improved media compatibility[1,2]
- Analog output
- Precision ASIC signal conditioning
- Calibrated and temperature compensated[3]
- SIL and DIP housings
- RoHS compliant



MEDIA COMPATIBILITY[1,2,3]

High pressure port: To be used with gases and liquids such as air, water, oil, which are compatible to the wetted materials (high temperature polyamide, ceramic AL_2O_3, epoxy, fluor silicone, glass, silicon).

Low pressure port: To be used with non-corrosive, non-ionic working fluids such as clean dry air, dry gases and the like.

SPECIFICATIONS

Maximum ratings

Supply voltage V_s	4.2 ... 5.5 V_{DC} max. 6.5 V_{DC}
Output current	
Sink	1 mA
Source	1 mA
Temperature ranges	
Compensated	5 ... +70 °C
Operating	-20 ... +85 °C
Storage[4]	-40 ... +125 °C

ELECTRICAL CONNECTION