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INTRODUCTION

α_2 -adrenoceptor agonists possess several beneficial actions during the perioperative period. They exert a central sympatholytic action, thus improving hemodynamic stability in response to endotracheal intubation and surgical stress, reducing the anaesthetic and opioid requirements, and causing sedation, anxiolysis and analgesia. Furthermore α_2 -adrenoceptor agonists may offer benefits in the prophylaxis and treatment of perioperative myocardial ischemia. The development of new, highly selective compounds which not only reduce anaesthetic requirements but induce anaesthesia by themselves may provide a new concept for the administration of anaesthesia (Figure 1).

FIGURE 1

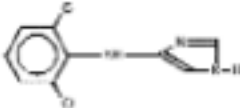
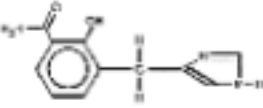
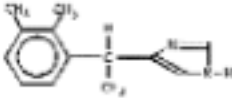
	$t_{1/2}$	α_2/α_1	Agonist
 Clonidine	9h	200	partial
 Mivazerol	4h	400	full
 Dexmedetomidine	2h	1600	full

Figure 1. - Structure and properties of α_2 -adrenoceptor agonists which have been used in anaesthesia. Clonidine is the prototypical α_2 -adrenoceptor agonist with an imidazole group. However, compared to more recently developed compounds it lacks specificity and full agonism at the α_2 -adrenoceptor. Mivazerol is a more specific agonist that has undergone phase III evaluation. Dexmedetomidine, the α_2 -adrenoceptor agonist with the highest specificity for the α_2 -adrenoceptor has been approved for clinical use in the USA since the end of 1999.

BASIC PHARMACOLOGY

Several kinds of α_2 -adrenoceptors have been classified into α_{2A} , α_{2B} , α_{2B} and α_{2D} receptor subtypes according to radioligand binding studies as well as pharmacological profiles. The classes correspond to the α_2 -C10, α_2 -C4, and the α_2 -C2 adrenoceptor subtypes according to their respective gene locations on chromosome 10, 4, and 2 (1). Common to most α_2 -adrenoceptors is their mediation of action through inhibitory guanine binding proteins (G_i -proteins). As a result the formation of cyclic adenosine monophosphate (cAMP) is reduced thus leading to changes in activity of various intracellular subsystems. However, not all actions of α_2 -adrenoceptor agonists can be accounted for by altered cAMP concentrations. Some of the effects of α_2 -adrenoceptor agonists are mediated by G-proteins that act directly on membrane-bound ion channels such as potassium channels. Further evidence exists that different α_2 -adrenoceptor agonists subtypes can be coupled to different or multiple second messenger systems.

α_2 -adrenoceptors are found in various body tissues. Within the central nervous system (CNS) spinal as well as supraspinal binding sites have been demonstrated mediating analgesic as well as sedative effects. In peripheral nerves clonidine has been demonstrated to produce nociceptive as well as antinociceptive effects (2). Most α_2 -adrenoceptors of the CNS are associated with noradrenergic pathways thus high receptor densities have been shown in the brain stem and especially in the locus coeruleus, the predominant noradrenergic nucleus of the brain. The locus coeruleus has been suggested to be involved in the establishment of vigilance. A decreased

activity of noradrenergic neurotransmission has been shown to reduce MAC of volatile anaesthetics (3). Other medullary binding sites of α_2 -adrenoceptor agonists have been at least partly attributed to imidazole receptors. These receptors have been demonstrated to mediate the antihypertensive and antiarrhythmic actions of α_2 -adrenoceptor agonists of the imidazole and imidazoline type such as clonidine, mivazerol and dexmedetomidine.

ROUTES OF ADMINISTRATION

Several different routes of administration of α_2 -adrenoceptor agonists have been described. Clonidine can be administered orally with a nearly complete absorption. The rectal administration of clonidine also results in a high bioavailability of 95%. Due to its lipophilicity and relatively small molecular size clonidine can also be administered transdermally. Intraoperatively or postoperatively α_2 -adrenoceptor agonists can also be given intravenously (i.v.), which is favourable in this setting.

SEDATIVE/HYPNOTIC PROPERTIES

α_2 -adrenoceptor agonists possess potent sedative properties depending on their specificity for the α_2 -adrenoceptor (Figure 2). From animal experiments it is known that clonidine reduces the minimal alveolar concentration (MAC) of halothane by up to 50% and dexmedetomidine by up to 90% (4). The reduction of anaesthetic requirements may be due to the sedative action of α_2 -adrenoceptor agonists as well as a direct interaction of some anaesthetics with central α_2 -adrenoceptors (5, 6). The anaesthetic sparing effect after dexmedetomidine administration is not restricted to animals but has also been demonstrated in humans. In a study involving 192 women undergoing abdominal hysterectomy three different treatment groups were examined. One group received just dexmedetomidine i.m. followed by placebo, the second group dexmedetomidine i.m. followed by fentanyl i.v. and the third group midazolam i.m. followed by fentanyl i.v.. It was demonstrated that the dexmedetomidine/fentanyl combination most effectively blunted the sympathetic activation during endotracheal intubation and reduced anaesthetic requirements. However, intra- and postoperatively dexmedetomidine treated patients showed significantly more bradycardia than patients receiving midazolam. Although the findings on a MAC reduction are differing for sevoflurane (7), a recent study reported a MAC reduction for isoflurane of about 40% after clonidine premedication (8). In addition, evaluation of effects on the electroencephalogram demonstrated significant decreases in spectral edge frequency, median power frequency and bispectral index (8).

FIGURE 2

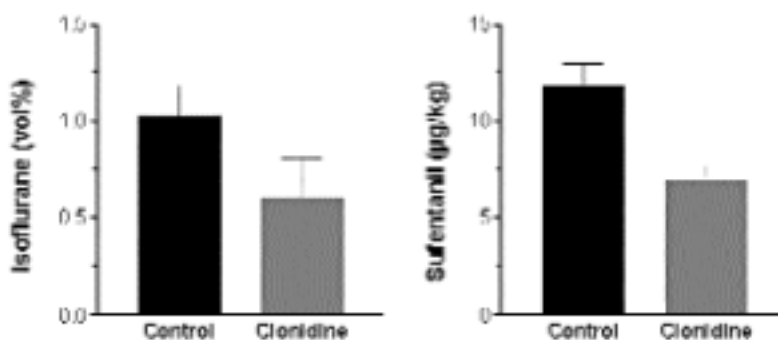


Figure 2. - α_2 -adrenoceptor agonists exert both sedative/hypnotic as well as opioid sparing effects in humans. When clonidine is administered preoperatively, anaesthetic requirements and analgesic requirements are reduced by about 40%. More specific compounds such as dexmedetomidine offer not only an anaesthetic sparing effect but produce anaesthesia by themselves. Data modified according to Ghignone et al.: *Anesthesiology* 1987, 67, 3-10; Flacke et al.: *Anesthesiology* 1987, 67, 11-19

However, α_2 -adrenoceptor agonists not only reduce the requirements of volatile anaesthetics but also that of intravenously administered anaesthetics (9, 10). Using the loss of eye-lid reflex as an endpoint for the induction of anaesthesia, it was shown that in diazepam plus clonidine premedicated patients the dose of thiopentone required to reach this endpoint was 20% less than in patients which received diazepam just by itself. Similar results were found for methohexitone and propofol. In a study comparing the effects of clonidine 5 $\mu\text{g}/\text{kg}$ with hydroxyzine 1 mg/kg it was found that intraoperative requirements of propofol were significantly reduced in the clonidine group.

Although bradycardia and hypotension occurred in the patients receiving clonidine there was no need for treatment. The clonidine group showed no delays in the recovery of psychomotor function and discharge from the recovery unit. An aspect that may be interesting in the future is that sedation and hypnosis brought about by α_2 -adrenoceptor agonists can be completely reversed by specific antagonists. Thus it is conceivable that future anaesthesia may use one injection for induction of anaesthesia and another for terminating the effect as needed, as it is already common in veterinary anaesthesia (Figure 3).

FIGURE 3

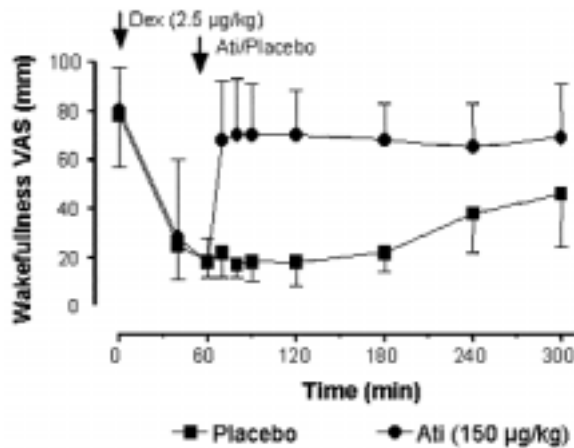


Figure 3. - The sedative/hypnotic effect of α_2 -adrenoceptor agonists such as dexmedetomidine (Dex) can be completely reversed by specific antagonists such as atipamezole (Ati). Data from humans, modified according to Scheinin et al.: *Anesthesiology* 1998, 89, 574-584

ANALGESIC EFFECTS

Apart from the potent anaesthetic sparing effects α_2 -adrenoceptor agonists also exert an analgesic and an opioid sparing effect. Clonidine premedication has been reported to markedly reduce intraoperative opioid requirements. In some studies an opioid sparing effect of up to 50% was reported (11). However, there are studies that did not observe this effect. This is possibly due to the fact that these studies were performed in patients undergoing coronary bypass surgery (CABG) receiving a high dose of an opioid, thus it is conceivable that a modest clonidine premedication did not alter the already maximal or supra-maximal opioid dosage. In a study in volunteers comparing the analgesic effect of dexmedetomidine with that of fentanyl, it was shown, that dexmedetomidine exerts a potent analgesic action by itself (12).

HAEMODYNAMIC EFFECTS

The hemodynamic effects of the α_2 -adrenoceptor agonist dexmedetomidine prohibit its administration as a rapid intravenous infusion or bolus. The activation of presynaptic α_2 -adrenoceptor agonists attenuates noradrenaline release thus reducing hypertension due to increased sympathetic activity. However, if administered rapidly or in large doses α_2 -adrenoceptor agonists mediate a transient vasoconstriction, which is now known to be mediated by an action on peripheral α_{2B} -adrenoceptors (13). Intravenous administration of potent α_2 -adrenoceptor agonists such as dexmedetomidine typically results in a biphasic response of mean arterial blood pressure (Figure 4). Dyck et al. demonstrated in healthy volunteers a rise of mean arterial pressure (MAP) five minutes after intravenous dexmedetomidine with a peak of 22% above baseline values (14). Heart rate (HR) concurrently decreased by 27% below baseline. After four hours MAP decreased by 20% from baseline values whereas HR showed a reduction of 5%. When administered intramuscularly the hemodynamic response to dexmedetomidine was less pronounced. The hemodynamic response to dexmedetomidine is similar to that already known from clonidine.

FIGURE 4

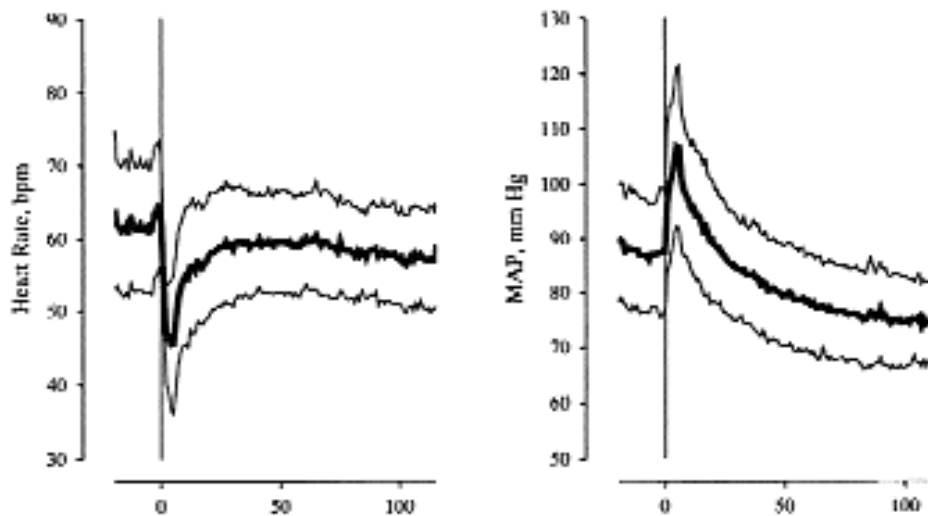


Figure 4. - Administration of a bolus dose of an α_2 -adrenoceptor agonist such as dexmedetomidine results in a biphasic haemodynamic response. Blood pressure increases transiently because of a peripheral action on α_{2B} -adrenoceptors followed by a mild decrease of blood pressure compared to baseline values, when the central sympatholytic action prevails. Heart rate drops initially, then increases again resulting in a mild bradycardia compared to baseline. Because of the transient effects bolus doses have to be avoided, potent α_2 -adrenoceptor agonists should only be administered via an infusion pump. Data modified according to Dyck et al.: *Anesthesiology*, 1993, 78, 813-820

ALPHA2-ADRENOCEPTOR AGONISTS IN CARDIAC RISK PATIENTS

Perioperative cardiovascular morbidity and mortality represent a major health care problem. Increased concentrations of catecholamines are among the main pathophysiological factors leading to perioperative myocardial ischemia. Modulation of sympathetic activity thus may be beneficial in preventing myocardial ischemia. In contrast to β -adrenoceptor agonists, which exert their antiischemic effects directly at adrenergic receptors of the heart, α_2 -adrenoceptor agonists reduce catecholamine levels due to their CNS effects without exerting negative inotropic effects. The α_2 -adrenoceptor agonist mivazerol has been shown to improve exercise-induced ischemia in patients with angina pectoris. α_2 -adrenergic agonists blunt the hemodynamic variability during anaesthesia, may exert antiischemic effects in the perioperative setting and may be effective as treatment for postoperative myocardial ischemia (15).

Of special interest is the effect of a perioperative reduction in sympathetic tone especially in patient with or at risk of a coronary artery disease (16). Using a small oral dose of clonidine (2 $\mu\text{g}/\text{kg}$) as a premedication it was demonstrated that the occurrence of new intraoperative myocardial ischaemic events as indicated by ST-segment deviations was reduced by about one third in patients undergoing CABG surgery (17).

The effects of a continuous infusion of dexmedetomidine were evaluated in high-risk patients undergoing vascular surgery. In order to provide adequate relief of surgical as well as postoperative stress, dexmedetomidine infusion was not stopped at the end of surgery but continued postoperatively for two days. The results suggest, that dexmedetomidine can safely be used in cardiac high risk patients if other drugs are administered to reduce the depression of heart rate and blood pressure. A trial on the effect of perioperative administration of mivazerol indicated that this α_2 -adrenoceptor agonist provides an effective and safe approach to reduce hemodynamic instability and myocardial ischemia in vascular surgery patients at high risk for adverse outcome (18). Since most studies employed only small numbers of patients, further trials including a large number of patients are currently being performed to evaluate the efficacy of α_2 -adrenoceptor agonists in the treatment of myocardial ischemia.

In high risk hypertensive patients undergoing major vascular surgery premedication with oral clonidine provided improved cardiac stability as well as reduced requirements of anaesthetics. Although blood pressure was reduced in the clonidine group compared to the placebo group, there was no difference in the need for the intervention with vasopressors. Administration of clonidine has been demonstrated to be safe even in patients at

high risk. When given preoperatively in CABG patients both the need for isoflurane and sufentanil was decreased. In addition, clonidine also appeared to improve renal function postoperatively possibly through its mild diuretic effect (19).

Several studies in CABG patients noted that intraoperative MAP was reduced after clonidine premedication, however, treatment was not necessary in all of these studies. Similarly, reductions in heart rate and also an increase in atropine treatment of bradycardia was published. There also exist reports, that clonidine premedication in CABG patients increases the need for cardiac pacing and vasopressor treatment in the post-bypass phase of CABG surgery. However, in a double blind placebo controlled study this was not confirmed (20).

POSTOPERATIVE SEDATION AND ANALGESIA

Morbidity and mortality in the intensive care unit (ICU) may be adversely affected by inadequate techniques for sedation and analgesia. The α_2 -adrenoceptor agonist dexmedetomidine may offer significant advantages for analgesia and sedation of patients requiring postoperative intensive care therapy. With a terminal half-life of 3.14 h, a steady state distribution volume of 173 L, and a clearance of 48.3 L/h the pharmacokinetic parameters of the patients on the ICU were comparable to those of volunteers, however, the distribution volume was lower in the volunteers (ranging from 88.7 to 102.4 L). In all patients the dosing regimen provided adequate sedation without any adverse effects.

Dexmedetomidine is licensed in the USA since the end of 1999 for postoperative intensive care sedation for up to 24h after surgery. In large multicenter phase III studies it was demonstrated that the administration of dexmedetomidine resulted in a dramatic reduction in the need for additional sedatives such as propofol and midazolam as well as for additional morphine. A similar but smaller study comparing propofol and dexmedetomidine was recently published involving 20 patients requiring sedation in the intensive care unit with a minimum of 8 h on the ventilator. Depth of sedation was monitored using the Ramsay scale and bispectral index monitoring and aimed to result at a Ramsay sedation level greater than 2. Both groups were similarly well sedated, however, in the propofol group patients needed three times more opioid analgesic compared to the dexmedetomidine group. In addition heart rate was reduced in the dexmedetomidine group. Despite the longer half-life of dexmedetomidine (dexmedetomidine: 100-150 min; propofol: 30-60 min) patients in both groups were extubated after similar and short recovery times. There was no adverse event in either group. Interestingly, even while on the ventilator, patients could be easily roused in the dexmedetomidine group and were cooperative. When interviewed after the end of the ICU stay using a Hewitt questionnaire only the dexmedetomidine treated patients were able to recall the length of stay accurately in contrast to those of the propofol group. The patients of the dexmedetomidine group experienced no unpleasant incidents and were not resentful of awareness. At moderate doses the sedative effects are unique because patients remain asleep when left alone, however, when aroused patients are cooperative and able to communicate and follow commands.

In contrast to most other sedatives and analgesics used on the ICU, dexmedetomidine has virtually no effect on respiration, even at high dosages. Thus dexmedetomidine can be used on the ventilator with spontaneous breathing techniques and administration of dexmedetomidine can safely be continued during and after extubation. Haemodynamics are stabilized, however a brief period of hypertension may occur after rapid administration. Maintenance doses result in reduced heart rates and blood pressure due to the central sympatholytic effect. Most sedatives such as propofol but also dexmedetomidine cause a drop in blood pressure due to vasodilation. The initial increase in blood pressure during dexmedetomidine administration can be circumvented by using a low rate for the loading dose. Overall a recent study showed no significant difference in haemodynamic effects when dexmedetomidine was compared to propofol.

Overall α_2 -adrenoceptor agonists appear to be safe drugs for sedation and analgesia in the intensive care setting. However, care must be taken that bradycardic arrhythmias as well as hypovolemia are contraindications for the use of dexmedetomidine. Bolus dosing has to be avoided when dexmedetomidine is used, since cardiovascular side effects such as temporary hypertension, hypotension and bradycardia may occur. These side effects are also known from the use of the less specific α_2 -adrenoceptor agonist clonidine. In some European countries clonidine is used quite often as an adjunct to other analgesics or sedatives. A recent survey of sedation and analgesia showed that clonidine is used in up to 90% of all intensive care patients. Compared to opioids, clonidine and dexmedetomidine exert virtually no respiratory depression and are thus especially indicated when spontaneous breathing patterns are aspired.

THERMOREGULATION

α_2 -adrenoceptor agonists have been demonstrated to alter the thermoregulatory response. In clonidine premedicated patients it was demonstrated that clonidine blunts the thermoregulatory response to changes in core temperature. Furthermore, clonidine has been demonstrated to reduce the incidence of post-anaesthetic shivering, to diminish established shivering and to increase the threshold for sweating. However, it has been hypothesised that clonidine may alter redistribution hypothermia occurring under general anaesthesia by its vasoconstrictive effect on peripheral vessels. In contrast, no effect of clonidine on redistribution hypothermia was found indicating that the effect of vasoconstriction on hypothermia is opposed by the central sympatholytic effect (21).

ALPHA2-ADRENOCEPTOR AGONISTS AS A NEW PARADIGM OF ANAESTHESIA

α_2 -adrenoceptor agonists are not only of interest because of their clinical effects but also because they open a new window to the understanding of the mechanism of action of general anaesthetics (22). Apart from pure α_2 -adrenoceptor agonists other compounds used in clinical anaesthesia bind to α_2 -adrenoceptors. It has been demonstrated that the intravenous anaesthetic etomidate interacts with cerebral α_2 -adrenoceptors and that an etomidate induced anaesthesia can partially be reversed by the use of the α_2 -adrenoceptor antagonist atipamezole thus indicating at least a partial action of etomidate through α_2 -adrenoceptors (6). Some opioids may also interact with α_2 -adrenoceptors. Meperidine binds and functionally inhibits α_2 -adrenoceptors at lower concentration than most other opioids. It was suggested that this interaction may explain the effectiveness of meperidine in the treatment of postanesthetic shivering (23). Binding of local anaesthetics to α_2 -adrenoceptors may provide a rationale for the increase of the effect of local anaesthetics at the spinal level in presence of α_2 -adrenoceptor agonists (24).

CONCLUSION

The utilisation of α_2 -adrenoceptor agonists adds an interesting new concept to the management of anaesthesia. Several beneficial effects listed in this review support the administration of α_2 -adrenoceptor agonist as a part of the drug armamentarium used in anaesthesia. However, there are side effects, most notably of haemodynamic nature, necessitating the continuing search for more specific substances.

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ABSTRACT

Anemia, which occurs commonly in ICU patients, is defined as a decrease in hemoglobin concentration to less than $13 \text{ g} \cdot \text{dL}^{-1}$ for a male adult or $12 \text{ g} \cdot \text{dL}^{-1}$ for a female adult [1]. Many patients admitted to an intensive care unit are anemic at the time of admission [2-4]; the majority of patients will become anemic during intensive care. Assuming normovolemia, the physiologic response to a decrease in hemoglobin concentration and oxygen content includes an increase of cardiac output and oxygen extraction by the tissues in order to meet tissue oxygen needs. If hemoglobin concentration is decreased below a critical value, tissue hypoxia occurs. Critically ill patients may present with 1) increased oxygen requirements (eg. due to impaired tissue oxygen utilisation) and/or with 2) a limited ability to adequately compensate for the low hemoglobin concentration. Not surprisingly, anemia is a risk factor for increased mortality in patients with preexisting cardiovascular disease or major blood loss. Consequently, it had been proposed that hemoglobin concentration in the critically ill should be maintained above a threshold of $10 \text{ g} \cdot \text{dL}^{-1}$ to ensure sufficient oxygen supply to the tissues. Augmenting oxygen content by the use of allogeneic transfusion was assumed to be associated with improved tissue oxygenation and, thereby, survival. According to recent investigations, allogeneic red blood cell (RBC) transfusion to ICU patients is commonly performed. Recent evidence is controversial regarding the influence of allogeneic RBC transfusion on the outcome of ICU patients. Liberal transfusion regimens resulting in greater hemoglobin concentrations may be associated with decreased survival. The latter may be due to an increased risk of adverse effects in the critically ill or to lack of efficacy. Extended storage of packed RBCs may be associated with an impaired ability to improve tissue oxygenation. At present, symptomatic treatment is recommended. The decision to transfuse or tolerate anemia should be based on a patient's individual cardiovascular reserve and on physiologic signs of impaired tissue oxygenation.

CAUSES OF ANEMIA IN PATIENTS RECEIVING INTENSIVE CARE

In general, anemia results from an increased turnover or reduced production of red cells. In the critically ill, causes of anemia include: surgical blood loss; repeated phlebotomies; blood loss into extracorporeal circuits; decreased red cell production and an impaired erythropoietin response [4][5]. Acute post-traumatic and / or intraoperative blood losses account for one third of RBC transfusions [4]. Anemia has been reported to be pronounced during acute renal failure and considerable amounts of blood are lost in extracorporeal circuits during renal replacement therapy [5]. Chronic blood losses include those generated by frequent diagnostic blood sampling. A recent estimate attributes approximately 30% of transfused RBCs to repeated phlebotomy [4;5]. Another common cause of anemia in this setting is gastrointestinal bleeding. This may be due to stress ulceration, anticoagulation or impaired gut mucosal integrity. A decrease in RBC life span to less than 120 days may be due to the use of extracorporeal circuits in renal replacement therapy, cardiac surgery and cardiac assist-devices, as well as by massive transfusion and hemolytic transfusion reactions.

Inappropriate formation of new red cells in the bone marrow may be another cause for anemia in the ICU. Normally, erythropoietin is produced within the kidney and liver in response to low arterial oxygen content. Erythropoietin release is impaired in the presence of acute renal failure. Proinflammatory cytokines (Interleukin 1β , Tumor necrosis factor α) have been shown to inhibit erythropoietin production, but may also directly interfere with maturation of red cells. Systemic inflammation decreases iron availability for RBC formation. Folate and vitamin B 12 deficiencies may also account for anemia in critically ill patients [5].

COMPENSATORY RESPONSE TO ACUTE ANEMIA

If normovolemia is maintained by fluid administration during acute blood loss, dilutional anemia results. The principal mechanisms which maintain adequate oxygenation of tissues in these circumstances are 1) an increase in cardiac output, which temporarily augments oxygen delivery during moderate hemodilution ($\text{Hb} > 10 \text{ g} \cdot \text{dL}^{-1}$) and 2) enhancement of tissue oxygen extraction [6] by redistribution of regional blood flow in according to regional oxygen requirements [6;7].