Introduction and Outline of the thesis
Introduction

This thesis describes the results from a randomized clinical intervention trial that ran between 2000 and 2003 at the Department of Obstetrics of the Academic Medical Center (AMC) and the VU University Medical Center (VUmc). Patients who were admitted with a severe hypertensive disorder of pregnancy at early gestational ages were asked to participate if they were eligible for a temporizing management strategy. After informed consent, they were randomized for a treatment strategy with plasma volume expansion or a treatment strategy without plasma volume expansion. These two options reflected the presence anno 2000 of the articulated dissensus among secondary and tertiary care obstetricians with regard to the treatment of choice.

Here, a historical background and an elaborate description of the trial design will be given.
Background

Hypertensive disorders of pregnancy are common, occurring in 7-10% of all pregnancies.\textsuperscript{1,3} It is generally assumed that deficient placentation is the pathophysiological basis, although the precise mechanisms remain unknown.\textsuperscript{5,6} Genetic\textsuperscript{7} and immunologic factors\textsuperscript{8,9} can play a role, as do pre-existing maternal factors.\textsuperscript{10} Through unidentified mechanisms endothelial dysfunction is the final common pathway to the clinical expression of the disease.\textsuperscript{11,12} However, the variation of clinical expression is extremely large, the recognizable aspects of endothelial dysfunction are not constant and it is not well known how this variation is mediated.

The clinical expression patterns show impressive variation between and within patients. Maternal expression ranges from pregnancy induced hypertension without signs of organ involvement, through preeclampsia (with proteinuria), eclamptic fits, and hemolysis elevated liver enzymes low platelets (HELLP) syndrome.\textsuperscript{1,2,13} The maternal syndrome is associated with significant maternal morbidity.\textsuperscript{14,15} Potentially life-threatening conditions such as liver rupture, eclampsia, renal insufficiency and cerebral bleeding may occur. In the Netherlands approximately 40% of maternal mortality is related to preeclampsia.\textsuperscript{16,17}

One of the inconsistencies of the deficient placentation hypothesis is the observation that fetal growth restriction only occurs if preeclampsia develops preterm, while birth weight in women with term preeclampsia is similar to controls without preeclampsia.\textsuperscript{18} In early preterm preeclampsia, fetal growth restriction is common, resulting in compensatory adaptation (brain sparing), and ultimately fetal death if no intervention is performed.\textsuperscript{19} The fetal/neonatal consequences are related to the gestational age when the syndrome occurs and prompts iatrogenic premature delivery. Severe neonatal morbidity (necrotizing enterocolitis, respiratory distress syndrome, infectious morbidity) may cause neonatal death or long term morbidity (retinopathy of prematurity, chronic lung disease, cerebral palsy or more subtle neurodevelopmental disabilities).

Management

Centralization of care for patients with severe disease or with very low expected birth weight is justified, given the high probability of iatrogenic premature delivery and the possibility of maternal complications requiring intensive care facilities.\textsuperscript{20} Delivery is the ultimate cure. However, at early gestational age, it is likely that temporizing management reduces neonatal morbidity, with limited, mostly reversible maternal morbidity.\textsuperscript{21-30} The mainstay of therapy until delivery therefore is symptomatic.
Prolongation of pregnancy requires close monitoring of both maternal and fetal condition to determine the optimal timing of delivery. At every evaluation fetal benefits and maternal risks of further prolongation of pregnancy have to be weighed against the benefits and risks of immediate delivery. The existing uncertainty in this respect is well demonstrated by the differences in criteria for delivery between hospitals around the world, but also within the Netherlands. Some may take the decision to deliver at the onset of symptomatic preeclampsia, while others only deliver for therapy-resistant hypertension, pulmonary edema or recurrent HELLP syndrome, when further prolongation of pregnancy may be hazardous for the mother. Fetal indications for delivery generally are repeated decelerations or prolonged low variability on fetal heart rate tracings. If a decision for delivery is anticipated within days, corticosteroid therapy for fetal lung maturation should be installed at an early gestational age.\textsuperscript{31} Sometimes, on the basis of very early gestational age and very low estimated fetal weight, a decision is taken by the parents, obstetricians and pediatricians to refrain from intervention when fetal distress becomes apparent. Fetal death is thus implicitly accepted, based on anticipated extremely poor neonatal survival.

**Symptom management**

Although the mainstay of temporizing (symptomatic) management is treatment of severe hypertension (see Chapter 1 for available drugs and indications), additional treatment of other symptoms is common. Magnesium sulphate is the superior alternative for the prevention and treatment of eclampsia.\textsuperscript{32-34} Headache or abdominal pain may be an expression of imminent pathology. Treatment with acetaminophen and/or morphine should be accompanied by adequate diagnostic strategies to detect the development of severe complications.

Reports that diminished circulating plasma volume, reduced cardiac output and end-organ vasoconstriction are key features of the syndrome received interest as early as the 1970s.\textsuperscript{35-44} The unstable hemodynamic system with decreased circulating plasma volume, dubbed by some as a state of ‘chronic shock’,\textsuperscript{41,45} was thought to be prone to hypotensive episodes in case of antihypertensive therapy, which in turn could induce organ hypoperfusion and fetal distress. To avoid this sequence, gradual lowering of blood pressure by antihypertensive medication is advised by some, while others advocated plasma volume expansion to allow for a faster decrease of blood pressure and a lower treatment target. It could be hypothesized that a lower blood pressure target might reduce the risks for maternal complications and the emergence of HELLP syndrome.
Reports documenting the hypothesized beneficial effects of plasma volume expansion stem from as early as 1972, but to date there is no solid evidence on the clinical value of plasma volume expansion. Literature is dominated by observational cohort studies, all of them biased by obvious or more hidden factors; the number of randomized trials is limited to three small sized studies, which did not use relevant clinical endpoints.

**Randomized trials**

Sehgal et al. compared 13 controls to 10 patients receiving the hyperosmolar dextran 40 and 9 patients receiving hyperosmolar plasmanate. Hemoconcentration decreased and urine output increased after two days of therapy with plasma volume expansion. Belfort et al. compared five patients who were randomly assigned to plasma volume expansion before vasodilator hydralazine therapy with five patients assigned to plasma volume expansion after hydralazine therapy. All patients showed low pulmonary capillary wedge pressure (a proxy measure for volume status) and high systemic vascular resistance before start of therapy. After plasma volume expansion with only 200 mL colloid plasma substitute (Haemaccel), wedge pressure had increased and resistance had decreased, blood pressure was unaffected. Lowe et al. reported that the infusion of Haemaccel led to a significant decrease in plasma albumin and hematocrit and an increase in atrial natriuretic peptide (ANP)-levels in 7 patients. These effects were not observed in the 8 control women who received hypotonic saline. These three trials did not compare clinical outcomes of management strategies with or without plasma volume expansion. Moreover, the numbers were too small, the type of hypertensive disease was too variable and the clinical relevance of the chosen outcomes was too limited.

**Observational studies**

Ozcan et al. and Nisell et al. demonstrated that ANP increase after a volume challenge was stronger in patients with preeclampsia than in normal pregnant patients, possibly due to decreased compliance of the capacitance vessels. A number of observational intervention studies measured cardiovascular parameters with invasive pulmonary artery catheters. They uniformly showed that plasma volume expansion leads to increased cardiac output, and decreased systemic vascular resistance. None of these studies reported the duration of these effects. Another study showed a short-lasting 1800 mL increase of plasma volume and an increase of central venous pressure after infusion of 500 mL of stabilized human serum half an hour after infusion. However, already 24 hours later this effect had completely disappeared. Several reports by Gallery et al. described significant improvement of high blood pressures that lasted for 48-72 hours after infusion of a plasma volume expander. Goodlin et al. described
several cases in which the syndrome was reversed, or at least temporarily improved.\textsuperscript{62} Brewer et al. specifically focused on the beneficial effect on diuresis in patients with oliguria in a set of 7 patients.\textsuperscript{63}

The association between decreased plasma volume and fetal growth restriction has been reported.\textsuperscript{37,42,64-70} Studies of fetal effects of plasma volume expansion demonstrated an improvement of flow velocity profiles in the umbilical artery, which was possibly associated with better perinatal outcome.\textsuperscript{71-73} Siekmann et al. demonstrated improved fetal blood flow parameters after maternal infusion of dextran, but not after infusion of NaCl.\textsuperscript{74} Another study demonstrated a similar effect on uteroplacental blood flow, measured with isotopes.\textsuperscript{38} This effect was not confirmed in two other studies using the same method.\textsuperscript{75,76} Two other studies that used Doppler flow velocimetry of the uterine artery, also showed no effect on uteroplacental blood flow. In one study colloid solution infusion was combined with the calcium antagonist verapamil, in the other a crystalloid solution was infused.\textsuperscript{77,78}

Only one study compared clinical outcomes (perinatal morbidity and mortality, maternal morbidity) between a management strategy with and without plasma volume expansion. It was a non-randomized retrospective matched-control study, and showed a non-significant improvement of perinatal outcome with plasma volume expansion.\textsuperscript{54}

In all observational reports, the study populations are selected, heterogeneous and small. Some are patients with chronic hypertension, or pregnancy induced hypertension, with or without proteinuria, and in some the type of hypertensive disorder of pregnancy is not defined. Additional morbidity is unclear in most cases. Also, the method of plasma volume expansion varies considerably. Apparently no consensus exists on the type of fluid or amounts to be administered; so far no dose-response studies have been published. The use of several agents has been reported. Colloid plasma substitute (gelofusine) has been used,\textsuperscript{49,72} pasteurized plasma (GPO) with a high albumin content,\textsuperscript{28,54,79} albumin 5\%,\textsuperscript{57} starch derivative solutions,\textsuperscript{71} Haemaccel,\textsuperscript{50} dextran,\textsuperscript{49} or crystalloids.\textsuperscript{52,53} Disadvantages of albumin and GPO are the high costs and the reported associated mortality compared to crystalloid fluids in critically ill patients with burns or hypoalbuminemia.\textsuperscript{80} Each agent has its specific advantages and disadvantages related to costs, and infectious capacity. A colloid agent frequently used for plasma volume expansion in patients with trauma, shock and sepsis is hydroxyethylstarch, which is a starch derivative. Advantages are low costs and low risks of transfer of infectious agents (prionic agents). In general, crystalloid solutions are considered less effective in a capillary leak syndrome. There is also no uniformity in ‘dosage’ that is the amount of plasma expansion. Some authors aim to achieve hemodynamic targets,\textsuperscript{50,54,72,79,81,82} others administer fixed amounts.\textsuperscript{49,52,53,57,71}
In our trial we opted for the use of a colloid solution, a choice predominantly based on two studies that compared the effects of colloid solutions with the effects of crystalloid solutions. The first study demonstrated more plasma volume expansion with a colloid in terms of higher ANP-production and hemodilution.\textsuperscript{51} In another study maternal and fetal hemodynamic parameters improved with dextran but not with NaCl 0.9%.\textsuperscript{74} Hydroxyethylstarch was the colloid solution of choice, because it is a solution of non-animal origin. The alternatives were predominantly on a gelatin basis. At the time of design of the study, these products would possibly be banned because of their increased risk of transfer of the agent causing bovine spongious encephalitis. This choice was further supported by a more recent randomized study, that demonstrated a decrease of hematocrit and diminished erythrocyte aggregation with Hydroxyethylstarch but not with NaCl 0.9%.\textsuperscript{83} In an animal model, Hydroxyethylstarch significantly improved microcirculation in sepsis, a situation similar to preeclampsia with regards to the capillary leak syndrome.\textsuperscript{84}

Adverse maternal effects of plasma volume expansion, such as pulmonary edema are recognized.\textsuperscript{48} Thus, when the maternal syndrome is severe, volume therapy should be guided by invasive hemodynamic measurements (Swan-Ganz catheter) to prevent pulmonary edema,\textsuperscript{28,35,85} accepting that this procedure too is associated with complications.\textsuperscript{86}

In summary, on theoretical mechanistic grounds, temporizing management with plasma volume expansion could be beneficial, resulting in improved maternal and fetal hemodynamics and improved perinatal outcome. However, in the absence of sufficiently powered randomized clinical trials, the clinical benefits, but also the risks of plasma volume expansion treatment remain ambiguous.\textsuperscript{47,48} In a survey among members of the International Society for the Study of Hypertension in Pregnancy, 42% of participants stated they used plasma volume expansion in the management of severe and early preeclampsia.\textsuperscript{87} From personal communication we judge this result to resemble the Dutch status quo at 2000.

Historically, in Amsterdam in the two university hospitals of the Academic Medical Center (AMC) and the VU University Medical Center (VUmc), management was distinctly different: the VUmc used plasma volume expansion on a routine basis, the AMC did not. In this local context, this stimulated discussion about the pros and cons of the use of plasma volume expansion.

Given the relevance of the problem, the impact of the syndrome and the genuine interest of the obstetric community, it was decided to engage in a randomized trial of a management strategy with plasma volume expansion and a management strategy without plasma volume expansion. The trial was funded by the Dutch National Health
Insurance Board (grant number OG98-021). After lengthy negotiations on feasibility and necessity of individual versus center randomization (the latter with both centers offering one treatment), individual randomization was finally agreed to. The results of this trial with clinical endpoints are presented in this thesis.

The trial

Study design
The study population was selected from all consecutive women presenting at a gestational age between 24 and 34 completed weeks who were admitted to the Departments of Obstetrics and Gynecology of the AMC and the VUmc. Both university hospitals are located in Amsterdam, The Netherlands and together serve as tertiary care centers for a community of approximately 2.5 million inhabitants (30,000 deliveries annually). During the study period, between April 1 2000 and May 31 2003, patients were eligible to participate in the trial, if they met at least one of the inclusion diagnoses: HELLP syndrome, severe preeclampsia, eclampsia, or severe fetal growth restriction with gestational hypertension (definitions in Table I).\textsuperscript{1,2,4} Overlap of clinical presentation within patients is frequent. To optimize generalizability of the study, patients were included across the spectrum of severe hypertensive disorders of pregnancy, with the intent of combined analysis, as well as predefined subgroup analysis. Patients with eclampsia were stabilized prior to randomization. Stabilization aimed to allow corticosteroid treatment for fetal lung maturation, but if a stable situation could be maintained, further prolongation of pregnancy was attempted and patients were eligible for the study.

<table>
<thead>
<tr>
<th>Table I. Definition of included hypertensive disorders</th>
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<tr>
<td>Severe preeclampsia\textsuperscript{1}</td>
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<td>HELLP syndrome\textsuperscript{2}</td>
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<td>FGR and pregnancy induced hypertension\textsuperscript{1,4}</td>
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<td>Eclampsia\textsuperscript{1}</td>
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Patients were excluded if severe fetal distress or lethal fetal congenital abnormalities were diagnosed; if language difficulties prevented informed consent, or if plasma volume expansion had already been given at the referring hospital. Patients already given antihypertensive or magnesium sulphate treatment were not excluded. Excluded patients received no plasma volume expansion.
After evaluation, information and informed consent the principal investigators (Wessel Ganzevoort and Annelies Rep, available 24/7) randomized patients between control (without plasma volume expansion) and treatment group (with plasma volume expansion) on a designated palmtop computer with random number generation software, within two strata of gestational age (between 240/7 and 296/7 weeks, between 300/7 and 336/7 weeks). The software concealed the group allocation until the patient details had been entered. Once randomized, the patient data could not be removed from the database. Gestational age was determined through the first date of last period, in most cases verified by a first-trimester ultrasound dating scan. The medical ethics committees of both hospitals approved the study.

**Study procedures**

Both management strategies were executed in both hospitals during an intensive run-in phase of six months with frequent consultation between trial staff to guarantee uniformity of procedures. After it was evaluated that both types of management could be safely performed in both hospitals, the study was started. During the study the trial study coordinators and principal investigators joined every two weeks to discuss emerging problems. If any issues regarding specific patient management arose between meetings, consultation by phone between centers took place. This synchronization of procedures was also performed between the staff of the Neonatal Intensive Care Units of both hospitals. Procedural decisions were in all cases directly documented, prior to outcome results became available.

The study outline is demonstrated in Figure 1. Blood pressure was measured by auscultation using a standard sphygmomanometer, and Korotkoff phase 5 for diastolic blood pressure. Magnesium sulphate therapy was used for prevention and treatment of eclampsia. Duration of treatment was 24-48 hours per episode. One course of corticosteroid therapy with intramuscular betamethasone (two doses of 11.4 mg with a 24-hour interval) was given when delivery was considered imminent before 32 weeks gestational age.

In the treatment group, a dose of 250 mL HydroxyEthylStarch (HES) 6% (200/0.5) was given twice daily over 4 hours. Restricted amounts of NaCl 0.9% were infused with intravenous medication in-between the infusions of HES. Fluid treatment was discontinued if clinical signs of pulmonary edema were observed. Antihypertensive medication was used to achieve a diastolic blood pressure between 85 and 95 mm Hg. The drug of first choice was ketanserine intravenously, a serotonin-receptor blocker. Additional medication (oral labetalol, α-methyldopa and nifedipine, and occasionally intravenous dihydralazine) was used when necessary. Nine patients with severe...
**Figure 1.**

**Inclusion criteria**
- HELLP syndrome  
  OR  
- severe preeclampsia  
  OR  
- eclampsia  
  AND  
- gestational age between 24 and 34 weeks

**Exclusion criteria**
- severe fetal distress requiring immediate delivery  
- lethal fetal congenital anomalies  
- language difficulties prohibiting informed consent  
- plasma volume expansion already given at referring hospital

**Informed consent and randomization**

**Treatment group**
- 2*250 mL HES 6% daily, restricted NaCl 0.9%  
- target diastolic BP 85-95 mm Hg  
- antihypertensive medication  
  - ketanserine intravenously  
  - a-methyldopa orally  
  - nifedipine orally  
  - labetalol orally  
  - occasionally dihydralazine intravenously

**Control group**
- restricted NaCl 0.9%  
- target diastolic BP 95-105 mm Hg  
- antihypertensive medication  
  - a-methyldopa orally  
  - nifedipine orally  
  - labetalol orally  
  - ketanserine intravenously  
  - occasionally dihydralazine intravenously

**Management**
- magnesium sulphate when deemed necessary by attending physician  
- corticosteroids for fetal lung maturation when delivery deemed imminent

**Fetal monitoring**
- fetal heart rate monitoring at least twice daily  
- fetal ultrasound assessment at least twice weekly

**Fetal indications for delivery**
- repeated decelerations on fetal heart rate tracings  
- prolonged low variability on fetal heart rate tracings

**Maternal indications for delivery**
- therapy-resistant hypertension  
- pulmonary edema  
- recurrent HELLP syndrome

**Primary outcome**
- Prechtl neonatal neurological examination score at term age

**Secondary outcomes**
- perinatal mortality  
- neonatal morbidity  
- maternal morbidity  
- pulsatility indices of fetal umbilical artery and median cerebral artery  
- neurodevelopmental testing at term age, three months and one year post term  
- psychosocial function at term age, three months and one year post term
preeclampsia and a gestational age below 30 completed weeks, were treated with plasma volume expansion under invasive hemodynamic monitoring, at the attending clinician’s decision.

In the control group, antihypertensive medication was targeted to achieve a diastolic blood pressure between 95 and 105 mm Hg. The drug of first choice was α-methyldopa. Additional medication (oral labetalol, nifedipine and intravenous ketanserine, and occasional intravenous dihydralazine) was used when necessary. Restricted amounts of NaCl 0.9% were infused with intravenous medication. The different blood pressure target ranges and choice of medication between groups reflect the hypothesized mode of action of plasma volume expansion. In practice, diastolic blood pressure after stabilization in both types of management is 95 mm Hg on average, and combination therapy was frequent.

Fetal heart rate monitoring was performed at least twice daily and fetal ultrasound assessment at least twice weekly. The estimated fetal weight ratio and birth weight ratio were calculated as the ratio of the estimated fetal weight or birth weight divided by the expected weight for gestational age (using the Gardosi customized growth chart p50-value, adjusted for maternal physiological variables). Children were considered small for gestational age if birth weight was below the 10th centile for gestational age. Fetal indications for delivery were repeated decelerations or prolonged low variability on fetal heart rate tracings. Maternal indications were therapy-resistant hypertension, pulmonary edema and recurrent HELLP syndrome.

**Maternal and perinatal outcomes**
The independent trial monitor committee consisted of two gynecologists and one pediatrician, who were not involved in the management of the study. This committee was blinded for treatment allocation insofar this was possible for an adequate review of the cases. Per protocol, the committee reviewed and classified all cases of maternal morbidity and fetal deaths after the 108th patient was included and after the ending of the trial. Fetal death was classified as intentional if, at the time fetal distress became apparent, and after discussion between the parents, neonatologists and obstetricians, a decision had been made to refrain from intervention. Unexpected fetal deaths were all classified as unintentional. At interim-analysis no differences between randomization groups were demonstrated and the study was continued. Neonatologists of both centers synchronized neonatal management strategies before the onset of the study. Two neonatologists, unaware of treatment allocation, reviewed and classified all individual cases of neonatal morbidity and mortality.
Main outcome measures and power calculation

The primary endpoint of the study was the Prechtl neonatal neurological examination score at term age (+/- one week). This contains a series of tests and the score equals the number of tests with an optimal response. The maximum score is 60 points, a score of 58 or higher is considered normal, a score of 53 or lower abnormal. Originally described in term infants, this neurological examination at term age, has also been shown to be a good predictor for neurological development in later life in preterm infants. Designated pediatric physiotherapists, who were unaware of treatment allocation, tested all children. The required sample size was calculated to be 216 (2 *108). This sample size, which took into account 30% loss to follow-up (perinatal death before term age or withdrawal), had 90% power to detect a difference of more than 2 points on the 60-point neurological examination test with a type I error of 0.05. We chose the 90% level to allow adequate power for subgroup analysis in this heterogeneous population.

Secondary endpoints were perinatal mortality, neonatal morbidity and maternal morbidity. Additional endpoints were the effects of plasma volume expansion on the pulsatility indices of the fetal umbilical artery and median cerebral artery and the effect of plasma volume expansion on maternal hemodynamic parameters. Additional follow-up was also planned. At term age, three months and one year post term children visited the outpatient department for neurodevelopmental testing. At these test moments the mothers filled out questionnaires regarding their psychosocial function. Finally, post-hoc analyses were planned to establish prediction models for adverse outcomes within this cohort, and to describe the dynamics of the syndrome and the timing of the onset of adverse outcomes.

The scope of this thesis is until one year post term. However, follow-up until 5 years post term is underway and follow-up until 10 years will be scheduled.

Role of the funding source

Supported solely by funds from the Dutch National Health Insurance Board (grant number OG98-021). The funding source had no role in the study design, data collection, data analysis, data interpretation, or the writing of the report. We acknowledge the scientific reviewers of the study who strongly supported the individual randomization, despite the considerable practical consequences; similarly we acknowledge the joint efforts of nursing and clinical staff to achieve procedural excellence in both treatments.
Outline of the thesis

All chapters contain a set of specific research questions, which is addressed, and described in the summary.

In **Chapter 1** an overview is presented of plasma volume regulation and blood pressure control mechanisms outside pregnancy, and of the changes in normal pregnancies and in pregnancies complicated by hypertensive disorders. Furthermore, the rationale of several hemodynamic interventions is discussed.

In **Chapter 2** and **Chapter 3** the main outcomes of the trial are presented.

In **Chapter 2** the effects of plasma volume expansion on maternal and fetal outcomes until term age are presented.

In **Chapter 3** the effects of plasma volume expansion on pulsatility indices of the fetal umbilical and middle cerebral arteries are presented.

In **Chapter 4** the outcomes at one year post term are presented with a special focus on factors in the disease process until term age that predict adverse outcome at one year.

In **Chapter 5** the psychological sequelae after severe and early-onset hypertensive disorders are described.

In **Chapter 6** an attempt is made to create a prediction model of adverse maternal and infant outcomes by factors present at admission.

In **Chapter 7** the incidence patterns of maternal complications are described.

In **Chapter 8** the relationship between underlying thrombophilic disorders and specific subtypes of the hypertensive disorders is described.

In **Chapter 9** the prevalence of abnormal General Movements and the association with abnormal neurodevelopmental outcome is explored.

In **Chapter 10** thoracic electrical bioimpedance is introduced as a non-invasive measurement method of hemodynamic changes.

In **Chapter 11** thoracic electrical bioimpedance is used for the monitoring of hemodynamic changes during plasma volume expansion.
Reference List


