AJNR

Mechanisms of MR signal alteration by acute intracerebral blood: old concepts and new theories.

L A Hayman, K H Taber, J J Ford and R N Bryan

AJNR Am J Neuroradiol 1991, 12 (5) 899-907
http://www.ajnr.org/content/12/5/899

Mechanisms of MR Signal Alteration by Acute Intracerebral Blood: Old Concepts and New Theories

L. Anne Hayman[1]
Katherine H. Taber[1]
Joseph J. Ford[1]
R. Nick Bryan[2]

We reviewed the current literature and theories pertaining to the appearance of hemorrhage on MR images. New theories were formulated to explain the etiology of spin-echo (SE) and gradient-echo contrast on clinical MR images of hematomas at low and intermediate field strengths. It is our hope that these theories will prompt further experiments to prove or disprove their validity. The discussion of SE contrast focuses on the powerful MR effects mediated by changes in protein concentration. These changes are postulated to occur as a result of (1) clot matrix formation; (2) settling of RBCs, which increases the number of RBCs per unit volume and the total protein concentration; and (3) alterations in *intracellular* protein concentration caused by changes in RBC hydration. The contribution of acid methemoglobin to image contrast via the proton electron dipole-dipole mechanism is also included. The discussion of gradient-echo contrast focuses on the inhomogeneity that may be present within voxels that contain a blood clot. This inhomogeneity results when the voxel contains regions with different magnetic susceptibilities (i.e., clumped RBCs and serum).

Two temporally arranged schemata for T2-weighted and T1-weighted SE scans are presented that illustrate how these factors might interact to explain the diverse appearance of hematomas on clinical SE images. The signal intensity on T2-weighted SE scans appears to be dependent primarily on the state of hydration of the RBC. This factor and the presence or absence of methemoglobin appear to be the major factors that govern contrast on T1-weighted SE images.

***AJNR* 12:899–907, September/October 1991**

The appearance of cerebral hemorrhage on clinical MR spin-echo (SE) images is complex, and a significant variability exists in the regional and temporal patterns described in the literature [1–8]. Gomori et al. [1, 2] have proposed an explanation only for the predominant MR signal intensity pattern at 1.5 T, but no theory has been offered to explain why a similar pattern has been described in hematomas imaged at intermediate and low field strengths [3–8]. The first section of this article addresses this issue by reviewing the factors that are known to influence T1 and T2 relaxation times. Also included are schemata that can be used to explain the clinical MR contrast patterns described in the literature.

The second part of this article addresses the unexplained diversity in the gradient-echo (GRE) signal intensity of blood by reviewing the factors that are known to influence GRE contrast. A theory is proposed that focuses on the macroscopic inhomogeneity that can occur within blood clots.

Contrast on SE Sequences

A retrospective analysis of clinical images has suggested that proton density may be an important factor that contributes to image contrast on the short TR/

Received March 7, 1989; revision requested August 14, 1990; revision received January 6, 1991; accepted February 11, 1991.

[1] Department of Radiology, Baylor College of Medicine, 1 Baylor Plaza, Houston, TX 77030. Address reprint requests to L. A. Hayman.

[2] Department of Radiology, Johns Hopkins University, Meyer 8-140, 600 N. Wolfe St., Baltimore, MD 21205.

0195-6108/91/1205-0899

short TE T1-weighted SE sequences [9]. This analysis used a "pseudodensity" ratio of hemorrhage to white matter of 1.5. However, spectroscopic experiments indicate that packed RBCs and the gray and white matter of brain have very similar proton densities (plasma = 1436, packed RBCs = 1000, white matter = 1070, gray matter = 1291). Thus, the true ratio would appear to be closer to 1.0, indicating that spin density has a minor role in the signal intensity of hematomas [10]. For this reason, our discussion focuses on changes in T1 and T2 relaxation times rather than proton density as an explanation for the contrast between hematomas and brain on short TR/short TE and long TR /long TE clinical SE sequences.

It is known that changes in T1 and T2 relaxation times can be caused by changes in protein concentration and/or the presence (or absence) of paramagnetic agents (deoxyhemoglobin or acid methemoglobin*). A summary of relevant spectroscopic studies concerning these observations is provided in Table 1 and the averaged relaxation rates (i.e., 1/T1 relaxation and 1/T2 relaxation) are shown in Figure 1 [13–29].

Influence of Protein Concentration

Although it has been known for some time that changes in protein concentration will alter the MR characteristics of aqueous solutions [20], this effect is minimal in very dilute solutions of protein (<6.1 g/l) [30]. However, T1 and T2 relaxation times in concentrated solutions decrease as the protein concentration increases [20, 31, 32]. In vivo, the protein concentration within clinical hemorrhages may be increased above that found in samples of whole blood or suspended RBCs in three ways: (1) by packing, which changes the number of RBCs per unit volume of blood; (2) by the formation and retraction of a clot matrix; and (3) by dehydration of the RBCs, which increases the intracellular hemoglobin concentration of the individual RBCs.

Increasing RBCs per unit volume.—Following in vivo hemorrhage, blood either clots or settles without clotting. In either event, the number of RBCs per unit volume increases. In settled blood, the cells are uniformly packed. In clotted blood they are clumped together by the action of platelets. Histologic studies of in vivo hematomas indicate that the clot may form as a single large homogeneous clump or, more commonly, as a number of smaller isolated focal clumps surrounded by lakes of serum (see Fig. 2) [33] (Alvord E, personal communication).

Several spectroscopic studies have demonstrated that increasing the number of RBCs per unit volume, in the absence of clot, shortens both the T1 and T2 relaxation times [16–20, 25–28]. This causes a decrease in signal intensity on long TR/TE T2-weighted SE images and an increase in signal intensity on short TR/TE T1-weighted SE images of packed RBC samples compared with RBCs suspended in a fluid. The effect of this change is probably insufficient to make blood hypointense relative to brain on T2-weighted SE images or hyperintense relative to brain on T1-weighted images unless other contributing factors are present (see Table 1 and Fig. 1 for comparison of packed RBCs with gray and white matter values).

Formation of a clot matrix.—During clot formation, the clotting factors in plasma convert soluble plasma proteins into a gel matrix. Serial MR imaging studies have shown a reduction in signal intensity on T2-weighted SE images when platelet contraction further concentrates the protein clot matrix. This has been observed in clots that do not contain RBCs [34], indicating that this contribution is independent of the MR changes caused by increasing the RBCs per unit volume. The observable differences in image intensity between the unretracted and retracted RBC-free clots on the T1-weighted and spin density–weighted SE images in the cited study indicate that a decrease in T1 relaxation time occurs during clot matrix retraction [34].

These changes may be the result of the decrease in free water and increase in cross linking between protein molecules that occur during clot matrix formation. A similar loss of signal has been noted on MR scans of sinuses containing dessicated sinonasal secretions [35]. Relaxation time measurements demonstrated that the T2 relaxation times of sinonasal secretions were greatly shortened when the secretions become viscid [36].

Alterations in RBC hydration.—When RBCs are sequestered in tissue, a series of complicated reactions occur that eventually lead to cell death and lysis. To the best of our knowledge, the details of this process in vivo have not been carefully investigated. However, it is known that in vitro the RBCs in blood clots lose their biconcave shape, and a substantial decrease in cellular diameter has been observed [37, 38].

Spectroscopic studies demonstrate that these alterations in RBC hydration have an effect on both the T1 and T2 relaxation times of blood [26, 27] (Taber et al., unpublished data). As RBC hydration is increased (i.e., the cells swell), both T1 and T2 relaxation times lengthen. Conversely, if RBC hydration is decreased (i.e., the cells shrink), both relaxation times shorten (see Table 1 and Fig. 1, which show the increase in relaxation rates 1/T1 or 1/T2 for dehydrated blood cells compared with oxygenated blood). In extreme cases, the T2 relaxation time can become so short that for a normal T1-weighted SE sequence there will be a sufficient T2 contribution to make the hemorrhage isointense or even hypointense relative to brain on T1-weighted SE images.

As the intracellular volume of individual RBCs changes (either by dehydration or overhydration), several factors that alter relaxation processes are present simultaneously. The number of RBCs that can settle into a given volume will be altered. Thus, in an area containing packed swollen RBCs, there will be fewer RBCs per unit volume and, therefore, *less* of the protein (hemoglobin) than in the same volume of blood comprising normally hydrated or dehydrated RBCs. Conversely, regions of dehydrated RBCs will have a greater total hemoglobin (i.e., protein) content because more RBCs can occupy the same volume. As previously discussed, increasing (or decreasing) the RBCs per unit volume changes the T1

* Like many proteins, methemoglobin has several ionizable groups. Although the acid-alkaline characteristics of methemoglobin are not fully delineated, the apparent pH of about 8.1 estimated by Austin and Drabkin [11] is consistent with the magnetic susceptibility measurements of Coryell et al. [12]. Below a pH of 8.1, the acid methemoglobin is a stronger paramagnetic agent than the alkaline methemoglobin, which is present at higher pH levels. Therefore, this article specifies acid methemoglobin throughout.

TABLE 1: Summary of Reported Relaxation Times and Rates of Blood Imaged at Field Strengths Less than 1.0 T

Sample/Tesla Value [Reference No.]	Temperature (°C)	T1 Relaxation Values			T2 Relaxation Values		
		Time (msec)	Rate (1/Relaxation Time [in sec])	Range	Time (msec)	Rate (1/Relaxation Time [in sec])	Range
Whole blood (intact)[a]							
0.02 [13]	35	303	3.3				
0.04 [14][b]	37	355	2.8	0.1			
0.06 [15]	23	372	2.7	0.2			
0.13 [16]	25	599	1.7				
0.14 [17]	37	656	1.5	0.1	275	3.6	0.3
0.15 [18]	–	571	1.8	0.1	261	3.8	0.2
0.20 [13]	35	909	1.1				
0.23[c]	37	1010	1.0		270	3.7	
0.23 [19]	37				316	3.2	0.1
0.25 [20]	37	800	1.3		205	4.9	
0.35 [21]	20				245	4.1	0.7
0.47 [22]	37	1300	0.8		320	3.1	
0.47 [23]	22	800	1.3	0.1			
0.47 [24]	24	902	1.1	0.1			
0.56 [15]	23	872	1.2	0.1			
Lysed blood (intact)[a]							
0.23 [19]	37				388	2.6	0.2
0.35 [21]	20				305	3.3	0.7
Whole blood (packed cells)							
0.13 [16]	25	382	2.6				
0.15 [25]	37	444	2.3	0.1			
0.23[c]	37	588	1.7		150	6.7	
0.23 [19]	37				168	6.0	0.4
0.24 [20]	37	550	1.8		160	6.3	
0.30 [26]	25	500	2.0	0.8			
0.55 [27]	25	556	1.8		170	5.9	
0.57 [28][d]	37				233	4.3	0.7
Lysed blood (packed cells)							
0.15 [25]	37	437	2.3	0.1			
0.23 [19]	37				212	4.7	
Overhydrated RBCs (intact)[a,c]							
0.23[c]	37	1497	0.7		551	1.8	
Overhydrated RBCs (packed cells)[f]							
0.23[c]	37	948	1.1		247	4.0	
0.30 [26]	25	710	1.4	0.2			
0.55 [27]	25	714	1.4		233	4.3	
Dehydrated RBCs (intact)[a,g]							
0.23[c]	37	482	2.1		63	15.9	
Dehydrated RBCs (packed cells)[h]							
0.23[c]	37	284	3.5		28	35.7	
0.55 [27]	25	400	2.5		100	10.0	2.4
Deoxyhemoglobin (intact)[a]							
0.13 [16]	25	599	1.7				
0.35 [21]	20				210	4.8	0.4
Deoxyhemoglobin (packed cells)							
0.57 [28]	37				217	4.6	0.6
Methemoglobin (intact)[a]							
0.25 [29]	37	417	2.4		147	6.8	
0.35 [21]	20				165	6.1	1.0
Gray matter of brain							
0.04 [14][b]	37	288	3.5	0.2			
0.06 [15]	23	332	3.0	0.2			
0.14 [17]	37	513	1.9	0.2	118	8.5	0.6
0.15 [18]	–	427	2.3	0.1	118	8.5	0.5
0.56 [15]	23	644	1.6	0.2			
White matter of brain							
0.04 [14][b]	37	238	4.2	0.2			
0.06 [15]	23	264	3.8	0.2			
0.14 [17]	37	242	4.1	0.3	86	11.6	1.3
0.15 [18]	–	262	3.8	0.1	113	8.9	0.9
0.56 [15]	23	469	2.1	0.1			

[a] Hemoglobin = 13–16 g/dl.
[b] In vivo data.
[c] Taber et al. (unpublished data).
[d] Data not included in averages used for Figure 1.
[e] About 77% water.
[f] About 77% water (Taber et al.), 70% water [26], and 71% water [27].
[g] About 50% water.

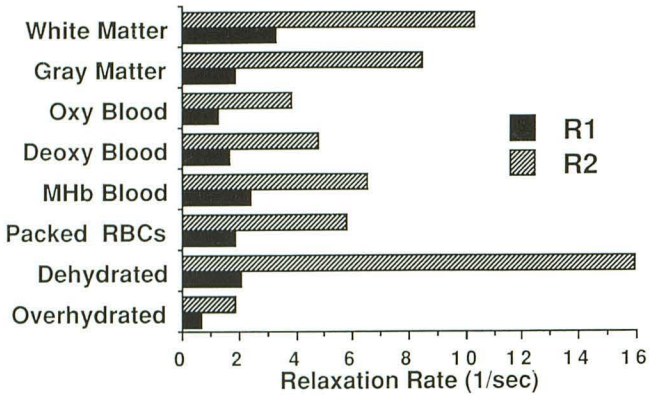

Fig. 1.—Average relaxation rates (R) obtained from Table 1 for brain and various formulations of blood. R1 is the inverse of T1 and R2 is the inverse of T2 (R1 = 1/T1 and R2 = 1/T2 with T1 and T2 in seconds). Therefore, on T1-weighted SE images, an increase in R1 causes an increase in signal. On T2-weighted SE images, an increase in R2 causes a decrease in signal. R values are useful because they can be added to obtain the overall relaxation rate for formulations of blood in which more than one factor contributes to the relaxation. Oxy Blood = oxyhemoglobin, Deoxy Blood = deoxyhemoglobin, MHb Blood = methemoglobin.

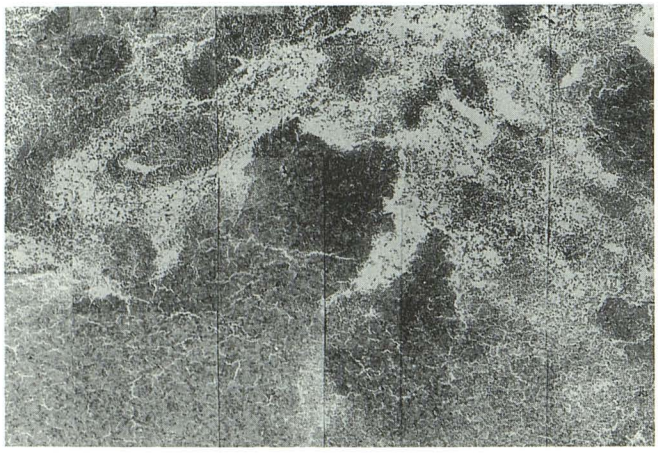

Fig. 2.—Macroscopic inhomogeneity. Montage of photomicrographs of a 7-μm-thick formalin-fixed blood clot that entrapped serum (in vitro specimen). The 2- by 2.5-mm region shown can be thought of as the cross section of approximately 4 voxels. This clot shows large intermingled regions of serum and densely packed RBCs. (Courtesy of J. B. Kirkpatrick, Baylor College of Medicine, Houston, TX.)

and T2 relaxation times by altering the total protein concentration of the sample (refer back to the section on increasing RBCs per unit volume) [16, 19, 20, 25–28].

In addition, a change in the hydration state of the RBC will alter the total protein concentration *within* each RBC. This change in intracellular protein concentration also affects T1 and T2 [20, 31, 32]. If changes in RBC volume produce a significant change in the intracellular hemoglobin concentration, the motion of the hemoglobin molecule will be altered. Shrinking RBCs increases their intracellular hemoglobin concentration. This causes crowding of the hemoglobin molecules, which restricts movement and slows down their tumbling rate [39]. This rate of tumbling is usually measured as a correlation time. Rapid molecular tumbling produces short correlation times and slower tumbling produces long correlation times. For protein solutions, longer correlation times (i.e., slower tumbling) produce shorter T1 and T2 relaxation times. However, in the clinical range of field strengths, changes in molecular tumbling alter T2 relaxation a great deal more strongly than T1 relaxation, resulting in a large selective T2 relaxation for dehydrated RBCs.

The selective effect on T2 relaxation results from the different relaxation mechanisms that determine T1 and T2 relaxation rates. Magnetic field dispersion (study of magnetic field dependence) curves for hemoglobin solutions indicate that both T1 and T2 are dominated by the secular (resonant frequency independent) component at and above clinical field strengths (>0.024-T MHz). For T1, the secular contribution from protein is much smaller than the secular contribution from water. Thus, T1 relaxation at and above clinical field strengths is dominated by the relaxation of water, and changes in protein have only a minor influence. This is not true for T2, which is dominated by the secular contribution from protein. Thus, changes in the correlation time of protein profoundly and selectively alter the observed T2 relaxation time (Koenig S, personal communication).

A fourth relaxation mechanism has recently been proposed that relies on the interaction of membrane components, particularly cholesterol, with water protons. These membrane components may exert a significant relaxation effect, enhancing especially the T1 relaxation of water protons [40]. Results that support the existence of this relaxation mechanism have been obtained from white matter brain samples [40], phospholipid vesicles [41], and cholesterol mixtures [42]. Cholesterol is hypothesized to be the important mediator of these effects [40]. Because RBC membranes also contain high concentrations of cholesterol [43], it is possible that some of the relaxation changes that have been noted clinically result from hydration and/or volume-mediated alterations in the interaction between water protons and the cholesterol of the RBC membrane. Thus, if changes in the molecular conformation of the RBC membrane occur when it shrinks or swells, these may alter membrane-dependent water relaxation and the MR signal intensities.

Influence of Paramagnetic Species

Gomori et al. [1, 2] proposed that the observed changes in signal intensity on T2- and T1-weighted SE images at high field strengths from acute hematoma were due to the presence of paramagnetic forms of hemoglobin that altered relaxation times by two distinct mechanisms. The first mechanism is a proton electron dipole-dipole (PEDD) interaction that occurs between the paramagnetic center and the protons of surrounding water molecules. The second mechanism is a selective T2 proton relaxation enhancement, which requires the compartmentalization of a paramagnetic agent within RBCs and the presence of extracellular water.

T1 and T2 influences due to PEDD.—The PEDD-dependent decrease in T1 and T2 relaxation does not require the packaging of paramagnetic hemoglobin within an intact RBC. Therefore, to evaluate the strength of the PEDD mechanism

alone, the relaxation times of lysed blood samples have been compared. In the clinical range of field strengths (0.19–1.4 T), there is no significant field strength dependence for the PEDD mechanism on T2 [21]. Thus, this factor is present to the same extent on T2-weighted SE images at all field strengths.

Spectroscopic studies indicate that acid methemoglobin is the form of hemoglobin that most significantly reduces T2 relaxation times via the PEDD mechanism over the clinical range of field strengths (0.19–1.4 T) [21]. However, the T2 relaxation time of lysed blood with a 100% acid methemoglobin saturation is *only* about 40% lower than that of fully oxygenated lysed blood [21]. Since this level remains above the measured T2 relaxation time for brain, the PEDD mechanism, even in the extreme case of 100% acid methemoglobin–enriched blood, cannot be the only factor that causes hemorrhage to appear hypointense on T2-weighted SE images. (The contribution of deoxyhemoglobin or alkaline methemoglobin is smaller than that of acid methemoglobin. Oxyhemoglobin has virtually no effect via the PEDD mechanism [21].)

The PEDD mechanism for T1 relaxation also is evident only for blood that contains acid methemoglobin. The details of this PEDD interaction are complex but appear to be a combination of outer sphere and contact interactions [39, 44]. The T1 relaxation for acid methemoglobin is mildly dependent on field strength in the range of 0.24–2.4 T [21], with the measured T1 relaxation time increasing only slightly with increasing field strength. However, because the T1 relaxation time of brain increases significantly across clinical field strengths, T1-dependent contrast between regions of acid methemoglobin–enriched blood and the adjacent brain increases with field strength. Thus, acid methemoglobin–enriched blood will appear progressively brighter than brain on T1-weighted SE images as the field strength of the magnet increases.

T2 influence due to T2 proton relaxation enhancement.—The second mechanism proposed by Gomori et al. [1, 2] was selective T2 proton relaxation enhancement. For this mechanism to be operative, the paramagnetic agent (deoxyhemoglobin or acid methemoglobin) must be confined within RBCs that are suspended in a fluid. Thus, the measured T2 relaxation differences between unclotted intact and lysed blood samples that contain suspended RBCs occur because T2 proton relaxation enhancement causes selective T2 relaxation, which further decreases the T2 relaxation time below the level caused by the PEDD mechanism. Two theories have been advanced to explain T2 proton relaxation enhancement. Both rely on the intracellular magnetic field being higher than the extracellular magnetic field owing to the presence of intracellular paramagnetic hemoglobin.

Gomori et al. [1, 2] have proposed that the T2 proton relaxation enhancement is due to water crossing the RBC membrane and thereby moving from one magnetic field to another. Bryant et al. [45] have pointed out that this mimics chemical exchange. According to Bryant et al., chemical exchange theory predicts that 1/T2 should have a linear relationship to hematocrit, which is not what is observed experimentally [45]. Another explanation was detailed by Thulborn et al. [46]. In their theory, the intracellular paramagnetic agent alters the magnetic field within the RBC, thereby generating local field gradients in the water around the RBCs. Diffusion of water molecules across these gradients during the time between echoes causes dephasing and a loss of signal that selectively decreases the T2 relaxation time [46, 47]. Thus, the loss of signal increases with increasing TE [21, 45, 46].

The degree of T2 relaxation caused by the mechanism of T2 proton relaxation enhancement is related to the proportion of extracellular water in the sample [46]. The maximal effect due to T2 proton relaxation enhancement occurs when there are approximately equal volumes of extracellular fluid and RBCs. Thus, physiologic changes in vivo can virtually eliminate the T2 relaxation caused by the mechanism of T2 proton relaxation enhancement if they profoundly decrease or increase the fraction of extracellular fluid. If the blood is concentrated by clotting or settling to levels greater than those of suspended RBCs, the removal of the extracellular water will greatly reduce the effects of T2 proton relaxation enhancement. When blood is diluted by CSF and does not settle, the increase in extracellular fluid will also greatly reduce the effect of T2 proton relaxation enhancement [48].

The selective effect of T2 proton relaxation enhancement is highly dependent on field strength. The reduction in T2 relaxation time varies as the inverse of the square of the field strength. Therefore, Gomori et al. [2] have proposed it as an explanation for the hypointense appearance of hematomas on T2-weighted SE scans at or above 1.5 T. Their theory predicted there would be little effect from T2 proton relaxation enhancement below 0.5 T.

In summary, T2 relaxation via the mechanism of T2 proton relaxation enhancement has been shown to be significant only when all four of the following conditions are met: (1) the use of high magnetic field strengths, (2) the use of long interecho intervals, (3) the presence of intact RBCs at moderate hematocrits (hemoglobin concentration of 13–16 g/dl), and (4) the presence of significant amounts of deoxyhemoglobin or acid methemoglobin [37].

Combined Effects of Paramagnetic and Protein Concentrations

Four factors have been identified that could significantly alter the MR appearance of clinical hematomas on low- and intermediate-field SE images. These are (1) the number of RBCs per unit volume, (2) the formation of a retracted clot matrix, (3) the hydration state of the RBC, and (4) the accumulation of acid methemoglobin. The overall effect on T1 and T2 relaxation times attributable to each factor will be determined by the degree to which each of these factors is present in vivo and the relative magnitude of the T1 and T2 relaxation changes caused by each factor.

The maximal changes in relaxation can best be estimated for three of the four factors (RBC concentration, RBC hydration state, acid methemoglobin accumulation) from spectroscopic data, which allow comparison of the changes in relaxation rate that occur when the state of the hemoglobin or protein concentration in blood is altered from the conditions present in flowing arterial blood (see Fig. 1 and Table 1). This

is possible because, unlike relaxation times, relaxation rates from different sources can be added to produce the total relaxation rate. Thus, $R_{total} = R_1 + R_2 + R_3 + \ldots + R_n$, where the subscripts represent different sources of enhanced relaxation (R). The data in Table 1 were obtained under a variety of conditions that can alter relaxation rates. Although these values were obtained by using different equipment and techniques, they allow a rough comparison of the impact of the various factors on the overall relaxation rate. The influence of clot matrix formation is not included because spectroscopic data on it were not available.

Inspection of the spectroscopic results (see Table 1 and Fig. 1) strongly suggests that at low and intermediate field strengths, small changes in RBC hydration cause sufficiently large changes in the relaxation rate to dominate the measured T2 relaxation rate and, therefore, the T2 relaxation time and, thus, the observed contrast on T2-weighted SE sequences. In fact, as was previously noted, the T2 relaxation time may become so short that it causes a decrease in signal intensity on even the T1-weighted SE images.

The number of RBCs per unit volume (i.e., packed cells vs intact blood with a hemoglobin content of about 13–16 g/dl) changes both the T1 and T2 relaxation rates by a few units. Thus, it has moderate impact on T2 and T1 relaxation (see Fig. 1). The PEDD effect of paramagnetic hemoglobin does not become a major factor in T2 relaxation until the field strength is significantly above the clinical range. However, the PEDD effect of acid methemoglobin is a major factor in T1 relaxation even at low field strengths (see Table 1 and Fig. 1).

Figures 3 and 4 show how all of these factors may interact to explain the diverse signal intensity patterns present on T2-weighted and T1-weighted SE images at low and intermediate field strengths [3–8]. Of course, evaluation of this theory awaits in vivo histopathologic and biochemical data.

Contrast on GRE Sequences

A number of factors influence the ultimate signal intensity on GRE images. Like SE images, GRE images are sensitive to the T1 and T2 properties of tissue. Thus, there will be variations in contrast on GRE images similar to those found on SE images related to the TR and TE used. However, signal intensity on GRE images must be influenced by other factors, since GRE and SE images with comparable TR and TE values are not identical [3, 6]. One difference is that GRE images generally do not use a 90° pulse to produce the signal, but rather use smaller flip angles, such as 15° or 30°. This

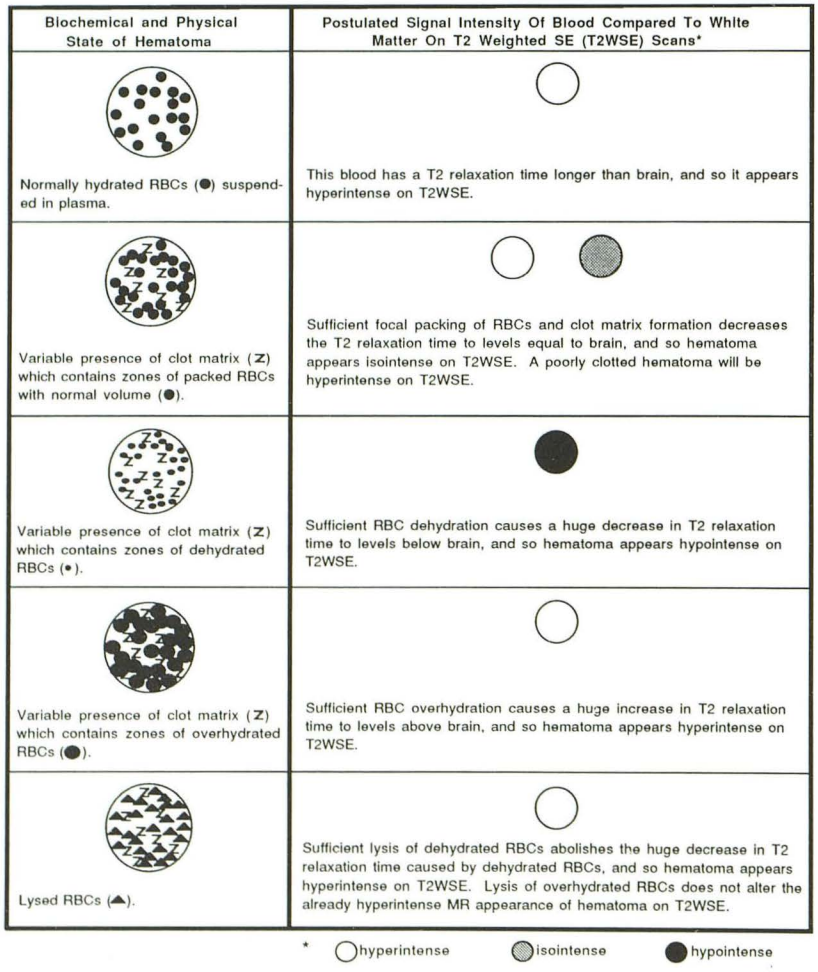

Fig. 3.—Temporally arranged schema illustrates the major signal intensity patterns observed on low-field clinical T2-weighted SE (T2WSE) images of intracerebral hematoma. On the basis of available spectroscopic data, we postulate that a hyperintense appearance on a T2WSE image obtained during the acute stage is indicative of poorly clotted blood. A hyperintense appearance much later could be caused by either RBC overhydration or by RBC lysis. A hypointense appearance is characteristic of dehydrated RBCs. Fully settled and clotted blood with normally hydrated or minimally dehydrated RBCs would be isointense relative to brain. The presence of intracellular or extracellular methemoglobin should cause only a mild decrease in T2 relaxation time. The ability of intracellular paramagnetic agents to alter this schema on high-field images has not been evaluated.

improves signal to noise when very short TRs are used, but it also reduces the amount of T1 contrast present in the image. While this alteration in contrast may be noticeable, it does not account for all of the unique properties of GRE images.

The most important difference between SE and GRE sequences is the method of echo generation. The RF pulse used to generate the echo in an SE sequence will refocus all sources of dephasing of the net magnetization, including magnetic field inhomogeneity due to both the imaging gradients and the inherent magnetic field, chemical shift differences, and magnetic susceptibility–induced effects. The only dephasing it cannot refocus is that due to nuclei changing their inherent resonant frequency between the 90° pulse and the echo from sources such as chemical exchange and diffusion or flow across a gradient. The GRE sequence relies on gradient reversal to generate the echo, and the only source of dephasing of the net magnetization that is refocused is the magnetic field inhomogeneity due to the imaging gradient. Since none of the other sources of dephasing will be refocused, they cause a reduction of signal intensity on the GRE image. Thus, GRE images are very sensitive to any sort of magnetic field inhomogeneity [47]. This is why GRE images contain artifacts at the boundary of materials with different magnetic susceptibilities, such as bone and air. It may also cause a profound reduction in the signal intensity of marrow within trabecular bone [49].

Histologic samples of acute hematomas in adults demonstrate that blood usually forms an "inhomogeneous" clot that rearranges the RBCs into tightly packed clumps of cells surrounded by pools of serum (consult Fig. 2 and the discussion on image contrast mediated by increasing RBCs per unit volume in the section on SE contrast). When both packed RBCs and serum occupy a voxel, the inhomogeneity should be sufficient to greatly reduce the signal from within the voxel and cause hematomas to be hypointense relative to brain on GRE images. This effect would be intensified at high magnetic field strength if the RBCs contain deoxyhemoglobin or methemoglobin. Conversely, hematomas that contain very large clumps of RBCs that homogeneously fill the voxel could

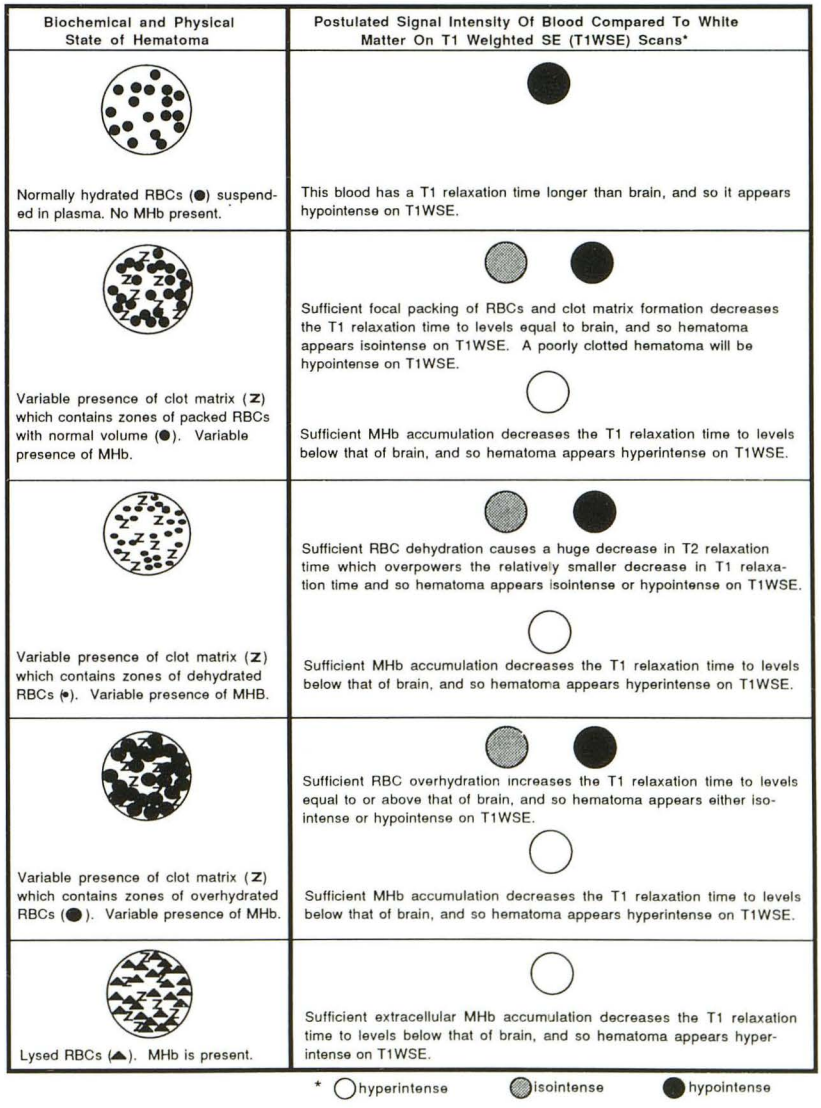

Fig. 4.—Temporally arranged schema illustrates the major signal intensity patterns observed on low-field clinical T1-weighted SE (T1WSE) images of intracerebral hematoma. On the basis of available spectroscopic data, we postulate that hyperintensity on T1WSE images indicates the presence of methemoglobin (MHb) in either an intracellular or extracellular location. Since T1WSE images are influenced by large changes in T2 as well as T1 relaxation times, a hypointense appearance on a T1WSE image obtained in the acute stage is indicative of either poorly clotted blood or the extremely short T2 relaxation time caused by RBC dehydration.

form the basis for the bright signal occasionally reported on GRE scans. Further research is needed to determine the significance of histologically documented clot inhomogeneity on GRE contrast of hemorrhage.

Conclusions

Four factors have a variable degree of influence on the signal intensity of hematomas on MR scans: clot matrix formation, changes in RBC concentration due to packing, changes in intracellular protein concentration due to changes in RBC hydration, and the effect of paramagnetic forms of hemoglobin. The degree to which each factor is relevant in vivo has yet to be determined.

Spectroscopy predicts the relative strength of these factors in changing the relaxation properties of unclotted arterial blood. Both RBC packing and clot matrix formation have been shown to reduce T2 relaxation times. The packing of RBCs produces a less pronounced reduction in T1 than in T2 relaxation times. The effect of clot matrix formation on T1 has not been quantified, but imaging experiments indicate a reduction in T1 occurs as retraction of the clot matrix proceeds.

Fluctuations in RBC hydration cause inverse changes in the concentration of intracellular hemoglobin. These changes in the RBC hydration have the ability to produce a profound, selective increase or decrease in T2 relaxation. On clinical images, the T2 change caused by RBC dehydration may dominate image contrast on both T2- and T1-weighted SE scans [50].

Only the PEDD effects of paramagnetic acid methemoglobin should significantly affect the signal intensity of hemorrhage on SE MR images obtained at intermediate and low field strengths. The effect of T2 proton relaxation enhancement is not present at low and intermediate field strengths and, therefore, is not a contributing factor in the appearance of hemorrhage on images acquired at these field strengths. Thus, the signal intensity on T2-weighted SE scans appears to be dependent primarily on the state of hydration of the RBC. This factor and the presence or absence of methemoglobin appear to be the major factors that govern contrast on T1-weighted SE images.

ACKNOWLEDGMENTS

We thank Elsworth Alvord, Department of Neuropathology, University of Washington, Seattle, WA, for personally reviewing adult human autopsy material with us; John J. Pagani for helpful review and comments; and Jackie Bogan for technical assistance.

REFERENCES

1. Gomori JM, Grossman RI, Goldberg HI, Zimmerman RA, Bilaniuk LT. Intracranial hematomas: imaging by high-field MR. *Radiology* **1985**;157:87–93
2. Gomori JM, Grossman RI, Hackney DB, Goldberg HJ, Zimmerman RA, Bilaniuk LT. Variable appearance of subacute intracranial hematomas on high-field spin-echo MR. *AJNR* **1987**;8:1019–1026
3. Seidenwurm D, Meng T-K, Kowalski H, Weinreb JC, Kricheff II. Intracranial hemorrhagic lesions: evaluation with spin-echo and gradient-refocused MR imaging at 0.5 and 1.5T. *Radiology* **1989**;172:189–194
4. Zimmerman RD, Heier LA, Snow RB, Liu DPC, Kelly AB, Deck MDF. Acute intracranial hemorrhage: intensity changes on sequential MR scans at 0.5 T. *AJNR* **1988**;9:47–57
5. Bydder GM, Pennock JM, Porteous R, Dubowitz LMS, Gadian DG, Young IR. MRI of intracerebral haematoma at low field (0.15T) using T2 dependent partial saturation sequences. *Neuroradiology* **1988**;30:367–371
6. Edelman RR, Johnson K, Buxton R, et al. MR of hemorrhage: a new approach. *AJNR* **1986**;7:751–756
7. Sipponen JT, Sepponen RE, Sivula A. Nuclear magnetic resonance (NMR) imaging of intracranial hemorrhage in the acute and resolving phases. *J Comput Assist Tomogr* **1983**;7(6):954–959
8. Sipponen JT, Sepponen RE, Tanttu JI, Sivula A. Intracranial hematomas studied by MR imaging at 0.17 and 0.02T. *J Comput Assist Tomogr* **1985**;9(4):698–704
9. Hackney DB, Atlas SW, Grossman RI, et al. Subacute intracranial hemorrhage: contribution of spin density to appearance on spin-echo MR images. *Radiology* **1987**;165:199–202
10. Woodard HQ, White DR. The composition of body tissues. *Br J Radiol* **1986**;59:1209–1219
11. Austin JH, Drabkin DL. Technique for the spectrophotometric study of diluted blood. *J Biol Chem* **1933**;100:x
12. Coryell CD, Stitt F, Pauling L. Magnetic properties and structures of ferrihemoglobin [methemoglobin] and some of its compounds. *J Am Chem Soc* **1937**;59:633–642
13. Koenig SH, Brown RD III, Adams D, Emerson D, Harrison CG. Magnetic field dependence of 1/T1 of protons in tissue. *Invest Radiol* **1984**;2(2):76–81
14. Smith FW. The value of NMR imaging in pediatric practice: a preliminary report. *Pediatr Radiol* **1983**;13:141–147
15. Ling CR, Foster MA, Hutchinson JMS. Comparison of NMR water proton T1 relaxation times of rabbit tissues at 24 MHz and 2.5 MHz. *Phys Med Biol* **1980**;25:748–751
16. Brooks RA, Battocletti JH, Sances A Jr, Larson SJ, Bowman RL, Kudravcev V. Nuclear magnetic relaxation in blood. *IEEE Trans Biomed Eng* **1975**;22(1):12–18
17. Jenkins A, Patterson J, Hadley DM, Condon BR, Teasdale GM. The use of in vitro magnetic resonance tissue studies to optimize pulse sequences in the imaging of intracranial haemorrhage. *Magn Reson Imaging* **1989**;7:395–403
18. Wolf GL, Conard B. NMR proton T1 and T2 relaxation times from fresh, in vitro canine tissues at 5.1 MHz. *Physiol Chem Phys Med NMR* **1983**;15:19–22
19. Hayman LA, Ford JJ, Taber KH, Saleem A, Round ME, Bryan RN. T2 effect of hemoglobin concentration: assessment with *in vitro* MR spectroscopy. *Radiology* **1988**;168:489–491
20. Fullerton GD, Potter JL, Dornbluth NC. NMR relaxation of protons in tissues and other macromolecular water solutions. *Magn Reson Imaging* **1982**;1:209–228
21. Gomori JM, Grossman RI, Yu-Ip C, Asakura T. NMR relaxation times of blood: dependence on field strength, oxidation state and cell integrity. *J Comput Assist Tomogr* **1987**;11(4):684–690
22. Rapoport S, Sostman HD, Pope C, Camputaro CM, Holcomb W. Venous clots: evaluation with MR imaging. *Radiology* **1987**;162:527–530
23. Sandhu HS, Friedmann GB. Proton spin-lattice relaxation time study in tissues of the adult newt *Taricha granulosa* (Amphibia: Urodele). *Med Phys* **1978**;5(6):514–517
24. McLachlan LA, Hamilton W. The effect of cancer on the spin-lattice relaxation time of mouse blood and tissue. *Biochim Biophys Acta* **1979**;583:119–128
25. Cohen MD, McGuire W, Cory DA, Smith JA. MR appearance of blood and blood products: an in vitro study. *AJR* **1986**;146:1293–1297
26. Sullivan SG, Stern A, Rosenthal JS, Minkoff LA, Winston A. NMR water-proton spin-lattice relaxation time of human red blood cells and red blood cell suspensions. *FEBS Lett* **1988**;234(2):349–352
27. Fabry ME, Eisenstadt M. Water exchange across red cell membranes: II. Measurement by nuclear magnetic resonance T1, T2 and T12 hybrid relaxation. The effects of osmolarity, cell volume and medium. *J Membr Biol* **1978**;42(4):375–378
28. Chuang AH, Waterman MR, Yamaoka K, Cottam GL. Effect of pH, carbamylation and other hemoglobins on deoxyhemoglobin S aggregation

inside intact erythrocytes as detected by proton relaxation rate measurements. *Arch Biochem Biophys* **1975**;167:145–150
29. Di Chiro G, Brooks RA, Girton ME, et al. Sequential MR studies of intracerebral hematomas in monkeys. *AJNR* **1986**;7:193–199
30. Hackney DB, Grossman RI, Zimmerman RA, et al. Low sensitivity of clinical MR imaging to small changes in the concentration of nonparamagnetic protein. *AJNR* **1987**;8:1003–1008
31. Brooks RA, Di Chiro G, Patronas N. MR imaging of cerebral hematomas at different field strengths: theory and applications. *J Comput Assist Tomogr* **1989**;13(2):194–206
32. Grosch L, Noack F. NMR relaxation investigation of water mobility in aqueous bovine serum albumin solutions. *Biochim Biophys Acta* **1976**;453:218–232
33. Darrow VC, Alvord EC, Mack LA, Hodson WA. Histologic evolution of the reactions to hemorrhage in the premature human infant's brain. *Am J Pathol* **1988**;130:44–58
34. Hayman LA, Taber KH, Ford JJ, et al. Effect of clot formation and retraction on spin-echo MR images of blood: an in vitro study. *AJNR* **1989**;10:1155–1158
35. Dillon WP, Som PM, Fullerton GD. Hypointense MR signal in chronically inspissated sinonasal secretions. *Radiology* **1990**;174:73–78
36. Som PM, Dillon WP, Fullerton GD, Zimmerman RA, Rajagopalan B, Marom Z. Chronically obstructed sinonasal secretions: observations on T1 and T2 shortening. *Radiology* **1989**;172:515–520
37. Alanen A, Kormano M. Correlation of the echogenicity and structure of clotted blood. *J Ultrasound Med* **1985**;4:421–425
38. Chin HY, Taber KH, Hayman LA, Ford JJ, Kirkpatrick JB. Temporal changes in red blood cell hydration: application to MRI of hemorrhage. *Neuroradiology* **1991**;33[Suppl]: 79–81
39. Lindstrom TR, Koenig SH. Magnetic-field–dependent water proton spin-lattice relaxation rates of hemoglobin solutions and whole blood. *J Magn Reson* **1974**;15:344–353
40. Koenig SH, Brown RD, Spiller M, Lundbom N. Relaxometry of brain: why white matter is bright in MRI. *Magn Reson Med* **1990**;14:482–495
41. Kucharczyk W, Lenkinski RE, Kucharczyk J, Henkelman RM. The effect of phospholipid vesicles on the NMR relaxation of water: an explanation for the MR appearance of the neurohypophysis? *AJNR* **1990**;11:693–700
42. Fralix TA, Ceckler TL, Wolff SD, Simon SA, Balaban RS. Lipid bilayer and water proton magnetization transfer: effect of cholesterol. *Magn Reson Med* **1991**;18:214–223
43. Lubin B, Kuypers F, Chiu D. Red cell membrane lipid dynamics. In: Brewer GJ, ed. *The red cell. Seventh Ann Arbor Conference. Proceedings of the Seventh International Conference on Red Cell Metabolism and Function*. New York City: Liss, **1989**:507–524
44. Koenig SH, Brown RD, Lindstrom TR. Interactions of solvent with the heme region of methemoglobin and fluoromethemoglobin. *Biophys J* **1981**;34:397–408
45. Bryant RG, Marill K, Blackmore C, Francis C. Magnetic relaxation in blood and blood clots. *Magn Reson Med* **1990**;13:133–144
46. Thulborn KR, Waterton JC, Matthews PM, Radda GK. Oxygenation dependence of the transverse relaxation time of water protons in whole blood at high field. *Biochim Biophys Acta* **1982**;714:265–270
47. Hardy PA, Kucharczyk W, Henkelman RM. Cause of signal loss in MR images of old hemorrhagic lesions. *Radiology* **1990**;174:549–555
48. Grossman RI, Kemp SS, Ip CY, et al. Importance of oxygenation in the appearance of acute subarachnoid hemorrhage on high field magnetic resonance imaging. *Acta Radiol* **1988**;139(S):56–58
49. Sebag GH, Moore SG. Effect of trabecular bone on the appearance of marrow in gradient-echo imagings of the appendicular skeleton. *Radiology* **1990**;174:855–859
50. Hayman LA, McArdle CB, Taber KH, et al. MR imaging of hyperacute intracranial hemorrhage in the cat. *AJNR* **1989**;10:681–686