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Bolus dynamics: theoretical and experimental aspects

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Abstract. This paper analyses the arterial enhancement produced by short intravenous boluses of iodinated contrast medium, with particular attention to the differences between various types of contrast media. A theoretical discussion is presented, followed by a small experimental study. The characteristics of the arterial time–attenuation curve are a function of the rate of contrast medium transit to the extracellular fluid (ECF), osmolality driven transit of water from the ECF into the plasma, direct effects on the heart and pulmonary circulation, the distribution of transit times in the cardiopulmonary circulation and recirculation. Theory predicts that while differences in peak arterial attenuation/peak height (PH) will be small, alterations in the areas under the time–attenuation curve (AUC) will reflect early-phase rate constants in the absence of major inotropic effects. The AUC should be higher for non-ionic than ionic media reflecting these lower rate constants. An experimental study on three healthy dogs confirmed these theoretical observations, with a slightly higher PH (6.5% higher) using a non-ionic medium but a substantially higher AUC (22% higher). (Differences significant at the 5% level, two-tailed paired *t*-test.) Our theoretical predictions and experimental findings suggest non-ionic media produce superior vascular enhancement, particularly shortly after injection. Possible clinical implications, particularly in dynamic enhanced computed tomography, are discussed.

Introduction

There is a widely-held belief that differences in pharmacokinetics between contrast media of different types are of no practical importance [1]. There are in fact good theoretical reasons why clinically important differences should exist, particularly in the short period immediately after intravenous injection, when contrast medium is primarily intravascular. The advent of faster CT machines, and particularly spiral CT, has heightened interest in this early phase of contrast medium delivery. Pharmacokinetic differences between contrast media may be much more important than is generally realized, particularly in early scanning. The advent of non-ionic dimeric agents may make these differences even more important.

Some theoretical and experimental observations are presented on the subject of contrast medium bolus dynamics. This we define as the study of time–attenuation curves observed in one set of vessels, such as the arteries, after injection of a short bolus of contrast medium into an "upstream" circulation, usually the systemic veins. Bolus "quality" can be measured by various indices, *e.g.* peak attenuation or curve height, all generally reflecting rapid delivery of the maximal amount of contrast medium. The production of a good quality bolus "downstream" is crucial in many areas of radiology. Examples include CT angiography, an area in which spiral CT has had a particular impact; indirect angiographic splenoportography; intravenous digital subtraction angiography (iv-DSA), and some forms of functional imaging where short fast boluses are crucial [2–5]. Furthermore, the study of bolus dynamics is a relatively simple process to model mathematically and offers insight into more complex processes such as the response to a prolonged or biphasic injection.

We have examined the hypothesis that pharmacokinetic differences between different types of contrast media affect bolus dynamics. We show that, *a priori*, differences would be expected in early imaging and have proceeded to an experimental investigation of this prediction. We have also examined the effect of changing injection rate on bolus quality, using a canine model and an ultrafast CT machine (Imatron C-100, Imatron Inc., South San Francisco, USA) which, with its subsecond scanning speed, can reliably quantify the passage of an aortic bolus.

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Bolus quality: theoretical aspects

Indices for assessment

Figure 1 illustrates the indices that are useful for assessing a vascular time–attenuation curve.

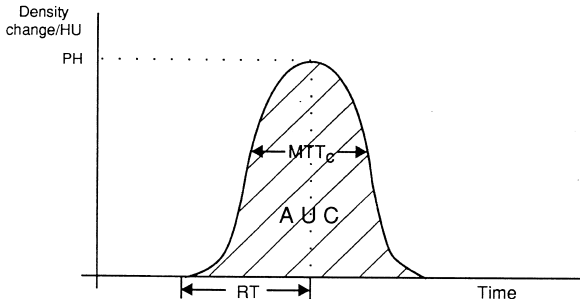


Figure 1. Ways of assessing a vascular time–density curve. AUC, area under curve; PH, peak height; MTT_c, curve mean transit time; RT, rise time.

Ignoring recirculation, bolus quality may be measured by the following.

Area under the time–attenuation curve (AUC)

If we can correct for recirculation, from classic dye dilution principles, this is proportional to the amount of iodine in the bolus divided by cardiac output (CO). The fundamental Stuart–Hamilton relationships may be restated as $AUC \approx D/CO \approx CBV/MTT$ where D is the amount of iodine in the bolus, CO the cardiac output, CBV the central blood volume (the volume of blood between the injection and sampling site) and MTT the mean transit time of the contrast bolus [6]. This holds provided that iodine concentration is linearly related to the attenuation increase, which is generally true in the absence of significant beam hardening.

Curve peak height (PH)

This is approximately proportional to the amount of iodine in the bolus D divided by the central blood volume CBV: the volume of blood between the injection and sampling site (Appendix A). Both the AUC and PH are closely related to the degree of vascular enhancement resulting from a contrast medium injection.

Curve mean transit time (MTT_c)

This is the time at which the centre of gravity of the time–attenuation curve passes, less the arrival time of the bolus, t_0. This is a measure of the curve "width". Intuitively it would seem reasonable to assume $AUC \approx PH \times MTT_c$ as was done by Burbank [6], but this does not always hold (section *Gamma variate curve fitting* below and Appendix B).

Rise time (RT)

This is the time from t_0, or arrival time, to the peak of the curve. In general we wish to maximize the AUC and PH for a given intravenous injection, since this would imply more overall enhancement. The importance of MTT_c and RT is less obvious; they should be short for most subtraction angiographic applications and some functional imaging techniques, but a long MTT_c might offer advantages for CT or non-subtracted conventional angiography as contrast medium will persist longer in vessels.

Before these indices are considered further, it is necessary to address the problem of correcting for contrast medium recirculation which is conventionally done using a "gamma variate" fit.

Gamma variate curve fitting

Iodinated contrast media are neither true first pass nor true intravascular agents. In practice, aortic time–attenuation curves have an initial maximum followed by a series of smaller peaks representing recirculation (Figure 2). The first pass phase is generally modelled by a gamma variate fit: that is by a curve of the form

$$C_a(t) = k(t-t_0)^a \, e^{(t-t_0)/b} \qquad (1)$$

where $C_a(t)$ is the increase in aortic CT number over baseline, t is time, t_0 is the arrival time of contrast medium at the aortic region of interest (ROI) and k, a and b are parameters of the fit. The gamma variate fit has been shown experimentally to give a good curve fit and to enable us to correct for recirculation [7].

For a gamma variate fit, the curve fit indices we have described above may be directly calculated: curve peak height $(PH) = k(ab/e)^a$; curve area $(AUC) = kb^{a+1}\Gamma(a+1)$ where $\Gamma(x)$ is the gamma function of x; rise time $(RT) = ab$; curve mean transit time $(MTT_c) = b(a+1)$.

It should be noted that the relationship $AUC \approx PH \times MTT_c$ cannot hold for a general gamma variate fitted curve (Appendix B) and cannot therefore be treated as a "strong" assumption.

Contrast medium passage through the lungs and heart

The aortic response to an intravenous bolus reflects several different processes. The first of these

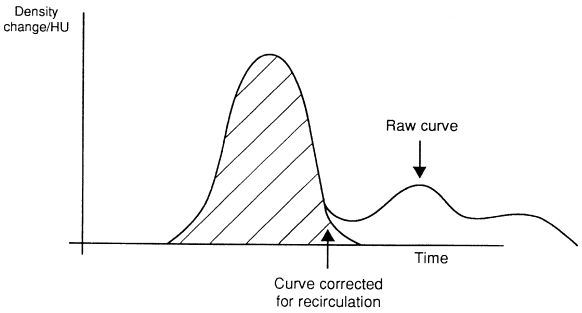


Figure 2. The use of the gamma-variate fit to correct for recirculation.

is the effect of transit through the pulmonary microcirculation and the cardiac chambers. Iodinated contrast medium filters rapidly into the extracellular fluid (ECF) and, conversely, hypertonic contrast medium induces passage of water from the interstitium into the plasma. This will tend to dilute the plasma iodine concentration. Secondly, differences in transit time through the cardiopulmonary circulation will broaden the plasma time–concentration curve. The heart and lungs effectively behave as a "linear system". Thirdly, the contrast medium may have an inotropic or chronotropic effect on the myocardium; this may affect the aortic time–concentration curve. We will consider these processes in turn and analyse their effects on the aortic time–attenuation curve.

Exchanges with the general extracellular space

Iodinated contrast media pass very rapidly from the intravascular to the extravascular space after injection [8–11]. The pharmacokinetics of contrast media is usually described using a two-compartmental open model where there is assumed to be first order transfer between a small central compartment and a larger peripheral compartment, with slower excretion [12–14] (Figure 3). For a short infusion of contrast medium, this leads to a biphasic logarithmic expression:

$$p(t) = Ae^{-\alpha t} + Be^{-\beta t} \quad (\alpha \gg \beta)$$

where t is time and $p(t)$ is plasma concentration at time t. (See Appendix C for a discussion.) α, which is large, represents the rapid-disposition rate constant and β, which is smaller, the slow-disposition rate constant. Note that the half time for slow disposition $t_{1/2,\beta}$, which approximately corresponds to renal excretion, is related to β by the relationship $t_{1/2,\beta} = \ln 2/\beta$. Similarly, the half time for rapid disposition, $t_{1/2,\alpha}$, is found as $\ln 2/\alpha$. During the early α-phase, in the first 2–3 min, transfer to the ECF is the dominant process in most tissues. During the much later β phase, it is renal excretion that predominates.

This two-compartmental formulation generally gives good agreement with observed data. There is, however, significant variability in the quoted values for α in the literature and the early phase of contrast medium pharmacokinetics remains incompletely understood. There are important experimental and theoretical reasons for this which merit brief discussion.

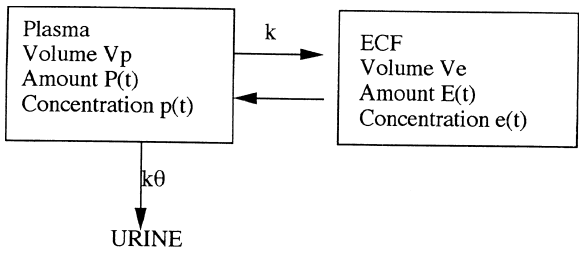


Figure 3. Two-compartment model defined in terms of mass transfer.

Experimental limitations to our understanding of early phase contrast medium pharmacokinetics include the practical difficulty of measuring rapidly changing data, particularly when a blood sampling technique is used. Secondly, pharmacokinetic researchers have tended to emphasize later (*i.e.* renal) aspects of excretion because of the obvious safety aspects. Where early phase α constants are calculated, they are often based on observations minutes rather than seconds apart [12]. There is relatively little directly comparative data in the literature on the very early phase of contrast medium pharmacokinetics, particularly in large mammals and especially in man. Thirdly, apart from the difficulties of measurement, at very early times, plasma is not a well mixed compartment. As has been described above, for several circulation times the vascular time–attenuation curve consists of a series of decreasing peaks. Conventionally, pharmacokinetic parameters are measured using a semi-log plot of plasma concentration against time and a "curve stripping" approach [14]. If this method is used, we should avoid data obtained before several circulation times have passed, but this fact is not always considered.

There are limitations to our understanding of early phase contrast medium pharmacokinetics at a theoretical level as well. Conventional drug pharmacokinetics analyses transfer of contrast medium molecules between compartments. The iodinated contrast media are, however, generally hyperosmolar compared with plasma. Their pharmacokinetics are consequentially unique in that for a complete analysis we have to examine not only diffusion of the contrast medium molecule into the interstitium, but also effects due to water drawn out of the interstitium by osmolality effects. A formal analysis of this leads to a set of non-linear differential equations for which exact solutions are difficult or impossible and which are best solved by iterative or approximate methods. This is an area which we are exploring in separate research using computer modelling. Furthermore, the two-compartment model is itself a simplification: in reality there are a large number of separate extracellular space compartments each with individual transfer constants. From first principles, however, non-ionic contrast media should have lower α values. This is because their lower osmolality and larger molecular size would cause both reduced osmolar disturbance and slower contrast molecule transfer to the ECF. This is borne out by the data of Jensen et al [14] which suggests 25% lower values, in a direct comparison in pigs,

of iohexol ($\alpha = 0.6\ min^{-1}$, $t_{1/2,\alpha} = 1.2$ min) compared with sodium/meglumine diatrizoate ($\alpha = 0.8\ min^{-1}$, $t_{1/2,\alpha} = 0.87$ min). This is, in turn, supported by other work suggesting non-ionic media are better retained in the vascular space [15, 16].

If $\alpha \gg \beta$, and renal excretion is ignored, $\alpha \approx 2k$ where k reflects the rate constant for contrast medium plasma/ECF transfer, assumed to be symmetrical for mass transfer (Appendix D). Thus, changes in α and k will be in proportion. It follows that values of k should also be about 25% lower for non-ionic media. It further follows (Appendix E) that dilution of the contrast bolus by passage through the pulmonary microcirculation should be less with non-ionic media, again by the same ratio of approximately 25%.

On theoretical pharmacokinetic grounds, the area under the aortic time–attenuation curve, after correction for recirculation with a gamma-variate fit (see above) should therefore be higher with non-ionic media. The relative alteration in area directly reflects the differences in early phase rate constants.

Peak attenuation is also proportional to the amount of iodine arriving in a bolus, and may thus be expected to be higher with non-ionic media. Basic geometric considerations would suggest that a small change in PH would produce a large change in AUC if curve shapes were unaltered. Therefore, we would expect changes in PH to be much smaller than the changes in AUC.

Transit time differences

Variability in transit times through the pulmonary circulation as the contrast medium disperses means that there is a lower limit to the curve width of the aortic bolus. From a mathematical viewpoint, this reflects the response of the pulmonary circulation to a δ-function input. There does not seem to be any reason why the distribution of transit times should be affected by the contrast medium molecule as this reflects the underlying physiology and anatomy of the relevant circulatory bed. Note, however, that absolute measurements of transit time would be prolonged if there was more iodine in the bolus. From the discussion above, then, MTT_c and RT would be longer for non-ionic media.

Note also that as we give faster and faster intravenous boluses of contrast medium, the progressive improvements in the aortic bolus will tail off. The aortic response will approach the "system response" imposed by cardiopulmonary and central venous transit.

Cardiac effects

Ionic media are more negatively inotropic than non-ionics, at least when given directly into the left heart or coronary circulation [17]. Experimental evidence suggests, however, that such effects are much reduced when right heart or intravenous injections are given [18]. From the discussion above, both the AUC and MTT are inversely proportional to cardiac output. If direct cardiac effects were significant, one would expect ionic media to be associated with larger areas under the aortic curve and longer transit times, thereby counteracting the permeability effects described above.

By contrast, experimental data suggest that peak height is almost independent of cardiac output, but inversely proportional to central blood volume [6]. Since ionic media would increase central volume more because of osmolality effects [19], peak height would tend to be lower with ionic media. Thus, both permeability and central circulatory effects would combine to decrease peak height with ionic media.

Theoretical aspects summarised

We are now in a position to attempt integration of these separate considerations. On theoretical grounds, non-ionic media should produce higher peak aortic concentrations and PH values because of permeability effects. The situation is less clear cut with the area under the aortic curve. If permeability effects outweigh inotropic effects, the areas under the aortic curve should be higher. If the inotropic effects are small, as expected for a venous injection, the differences in curve area should reflect differences in the values of α for ionic and non-ionic media. The examination of the AUC thus provides a powerful tool for analysing a complex process.

Experimental method

The subjects were three male mongrel dogs weighing 34.5, 35.5 and 35.4 kg. All were healthy with normal biochemical and urinary profiles. Anaesthesia was induced using a 2.5% solution of thiamylal sodium ("Surital", Parke Davis, Morris Plains, NJ, USA) and maintained with intermittent injections. An endotracheal tube was inserted and mechanical ventilation performed with a Harvard ventilator. 9 French central venous catheters were placed via an internal jugular vein approach. Continuous ECG was performed. Arterial pressure monitoring was performed through catheters placed via the femoral arteries.

In two dogs 15 ml of sodium-meglumine diatrizoate ("Renografin", ER Squibb, Princeton, NJ, USA) and iohexol ("Omnipaque", Sanofi Winthrop Pharmaceuticals, New York, USA), both at 292 mgI ml^{-1} of iodine concentration, were injected at 5, 10 and 20 ml s^{-1} via the central venous catheter. The diatrizoate used was stock "Renografin 290" and the iohexol was stock "Omnipaque 300" diluted with sterile water to

render it to 292 mgI ml^{-1} strength. Both were warmed. The boluses of diatrizoate were given prior to iohexol in one dog, while the second dog received iohexol first. In the third dog, 25 ml of iohexol 300 mgI ml^{-1} and diatrizoate 292 mgI ml^{-1} were given at 10 and 20 ml s^{-1}. In all cases, the lines were flushed prior to injection so that any "dead space" was filled with the same contrast medium as was present in the pump.

Scanning was performed using an Imatron C-100 ultrafast CT machine. 20 sequential 0.1 s duration axial sections were obtained at the mid abdominal aorta over 30 s. The dogs were paralysed and ventilated and respiration was suspended for the duration of the scan, after prior hyperventilation.

Using the on-line Imatron software, time–attenuation profiles were drawn for an aortic ROI. The data were corrected for recirculation using a gamma-variate fit. The previously described indices were measured: (i) AUC; (ii) PH; (iii) MTT_c; (iv) RT.

MTT_c was calculated by subtracting the arrival time from the calculated value for curve mean transit time. With eight of the curves, the fitting was repeated on a separate occasion to verify reproducibility.

Significance between paired sets of data was examined by performing a logarithmic transformation and using paired *t*-tests (two-tailed) on a standard software package ("Statview II", BrainPower Software, Calabasas, CA, USA). This was done after taking advice from a professional medical statistician.

All work was performed in accordance with the rules and procedures of the University of Chicago Institutional Animal Care and Use Committee.

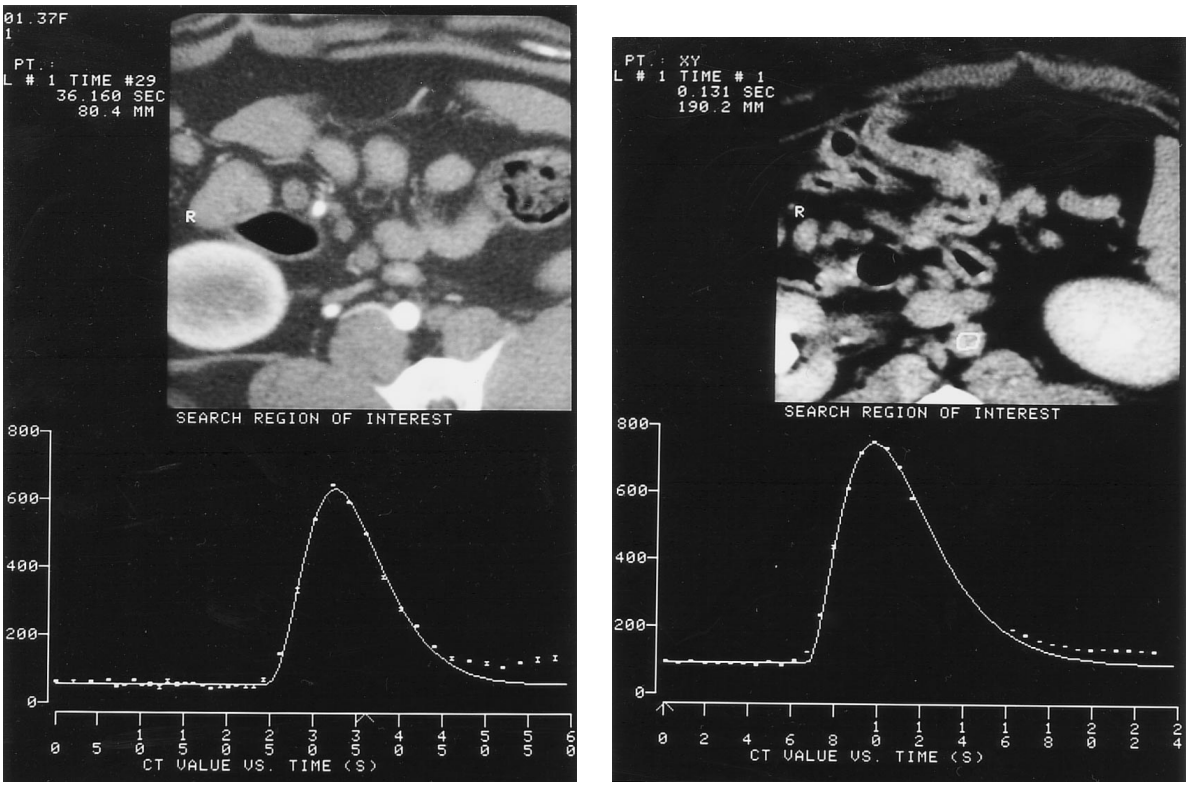
Results

Typical curve fits are illustrated in Figure 4. Curve fits were highly reproducible. The maximum difference in any of the three parameters examined for a given injection was 3% with a standard error of mean 0.3%. Results are summarised in Tables 1–3.

Using non-ionic contrast medium increased the AUC, PH and MTT_c (all differences significant, $p < 5\%$). RT was also prolonged ($p < 10\%$). The area under the curve increased by a mean of 22%, the peak attenuation by a mean of 6%, the rise time by 19% and the mean transit time was lengthened by 7% (Figure 5).

Using a 10 ml s^{-1} injection rate compared with 5 ml s^{-1} increased PH and decreased MTT_c and RT ($p < 5\%$). There was no significant change in the area under the curve, AUC. The mean rise in PH was 8% and the mean falls in MTT_c and RT were 36% and 54%, respectively.

Using a 20 ml s^{-1} injection rate compared with 10 ml s^{-1} decreased PH by 5% (difference



(a) (b)

Figure 4. (a) and (b) Two examples of curve fits to aortic time–attenuation curves. In both cases regions of interest have been drawn in the aorta.

Table 1. Ionic (diatrizoate) compared with non-ionic contrast media (iohexol)

	Difference significant	Ionic (mean)	Non-ionic (mean)	Mean % difference
AUC	$p<5\%$	1370 HU s	1690 HU s	22%
PH	$p<5\%$	270 HU	287 HU	6.5%
MTT_c	$p<5\%$	4.30 s	5.13 s	16%
RT	$p<10\%$	2.98 s	3.6 s	18%[a]

[a] Non-significant result.

Table 2. Injection rates of 5 ml s^{-1} *versus* 10 ml s^{-1}

	Difference significant	5 ml s^{-1} (mean)	10 ml s^{-1} (mean)	Mean % difference
AUC	Not significant			
PH	$p<5\%$	267 HU	413 HU	8%
MTT_c	$p<5\%$	5.83 s	3.14 s	−36%
RT	$p<5\%$	4.19 s	2.81 s	−54%

Note that differences in the absolute values of the PH, MTT_c and RT between the 5 ml s^{-1} and the 10 ml s^{-1} injections may reflect a different range of injection volumes as well as differences in the injection rates. Absolute values have been quoted for completeness, but the last column, listing the mean proportionate difference, is likely to be a better guide to the effects of changing injection rate.

Table 3. Injection rates of 10 ml s^{-1} *versus* 20 ml s^{-1}

	Difference significant	10 ml s^{-1} (mean)	20 ml s^{-1} (mean)	Mean % difference
AUC	Not significant			
PH	$p<10\%$	413 HU	388 HU	−5%[a]
MTT_c	Not significant			
RT	Not significant			

[a] Non-significant result.

significant $p<10\%$). There were no other significant differences. The higher injection rate decreased AUC by 15%, but this was not significant.

Discussion

Iohexol produces curves with an AUC 22% higher than diatrizoate. This is a small study but, following the theoretical discussion above and given the 25% differences in α quoted by Jensen et al [14], it strongly suggests that non-ionic media are better retained in the vascular space than ionic media and self-dilute to a lesser degree by a factor of about a quarter. It also suggests that, at least for a venous injection, any effects on bolus geometry from cardiac effects are small. The fact that our relative differences in α are slightly less than Jensen et al's may, however, reflect the confounding factor of cardiac effects. Alterations in peak height are much smaller (6.5%.) As discussed before, this is not surprising, as geometric considerations would suggest that a small change in PH would produce a large change in AUC. Changes in PH may be thus seen as the tip of an iceberg reflecting quite substantial differences in pharmacokinetics. The observation that non-ionic media may produce slightly higher levels of vascular enhancement in diagnostic doses has been made before [20], but has perhaps received little attention from the general radiological community. This is surprising, particularly in view of the advent of non-ionic dimers (which may extend this advantage) and the increased interest in imaging techniques such as CT angiography where maximizing vascular contrast attenuation over 30–40 s is crucial.

Note that this argument may be turned on its head if we are using contrast medium for parenchymal, as opposed to vascular, enhancement. It may be predicted that ionic media, being more rapidly distributed to the ECF, could possibly offer advantages in parenchymal imaging. It is therefore of interest that Chambers et al, in comparing ionic and non-ionic media, found greater hepatic parenchymal enhancement with the ionic medium iothalamate as opposed to the non-ionic iopamidol [21]. This was despite the dose of iodine being higher with iopamidol (282 mgI ml^{-1} *versus* 300 mgI ml^{-1}. As we have pointed out before, this can be predicted from pharmacokinetic consider-

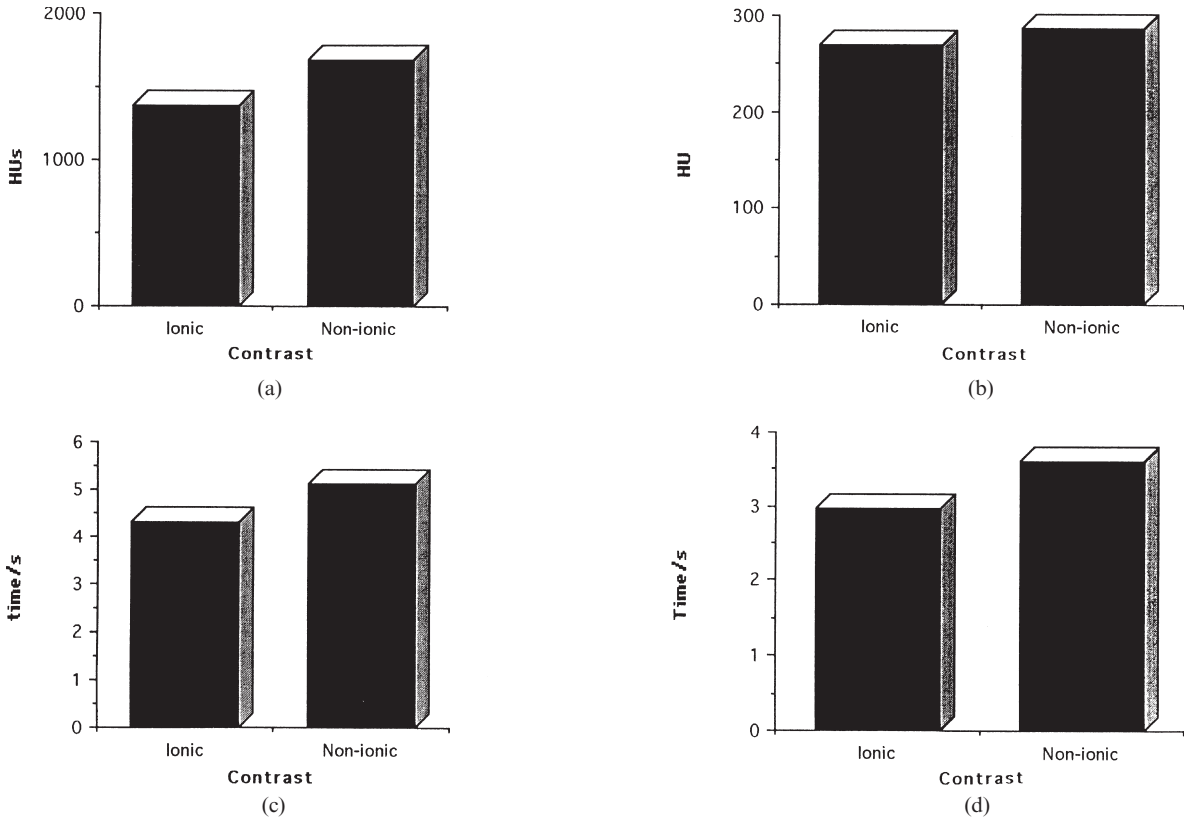


Figure 5. Graphical summary of the differences between ionic and non-ionic media. (a) AUC; (b) PH; (c) MTT_c; (d) RT.

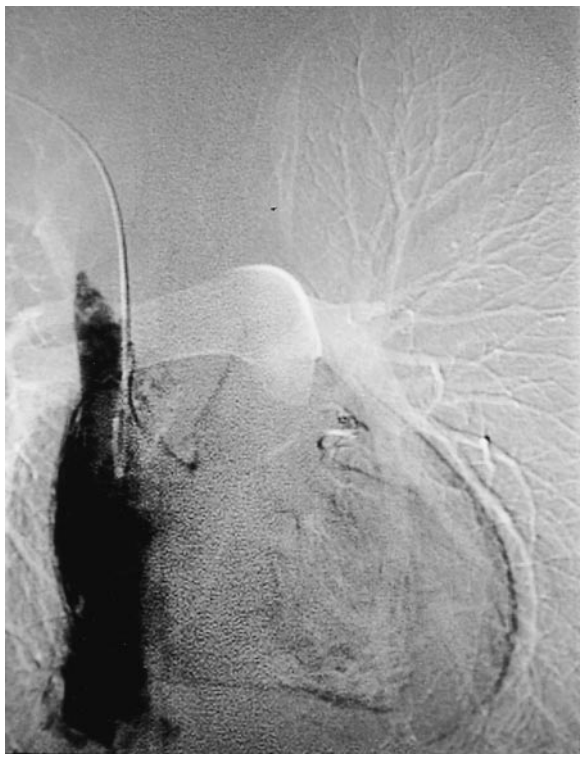


Figure 6. Digital subtraction angiogram after injection of contrast medium through a pigtail catheter in the right atrium. Note the reflux down the inferior vena cava.

ations as hepatic enhancement significantly reflects interstitial as well as vascular enhancement [22]. Chambers also found the non-ionic medium produced a mean 10% higher aortic enhancement and a mean 18% higher portal venous enhancement. This is despite the iodine concentration being only slightly higher (6%) and supports our findings on the superiority of non-ionic media for vascular imaging.

Non-ionic media may therefore offer a slight disadvantage in imaging liver metastases as lesion conspicuity depends on differences in extravascular diffusion [23]. Metastases, in which diffusion is usually slower, may stand out more from normally enhancing liver parenchyma with ionic media as they distribute rapidly to the ECF.

There is a slightly longer transit time and rise time with non-ionic contrast media. This may simply be because there is more contrast medium in the bolus. The differences observed (16 and 18%) appeared to parallel alterations in AUC. Transit time differences may also reflect differences in viscosity, an additional parameter which we have not discussed in our theoretical analysis.

The broadening of the contrast time–attenuation curve by cardiac and lung transit sets a limit for bolus quality. A more rapid injection rate (10 ml s^{-1} as opposed to 5 ml s^{-1}) helps in approaching

this limit. However, too fast an injection (20 ml s^{-1}) not only does not help, but has a tendency to cause a deterioration in bolus quality. We suspect that this reflects both the mathematics of a "linear system" and also reflux on very fast injection. Figure 6 illustrates the effects of a fast injection of contrast into the right atrium during iv-DSA in a clinical human study. Considerable reflux into the superior and inferior vena cava can be seen. This refluxed contrast medium would consequently have a lengthened transit time.

Our results echo the earlier work of Claussen et al who also demonstrated that there was little practical advantage in giving intravenous contrast medium injections at rates above 8 ml s^{-1} [24].

In conclusion, non-ionic media may offer significant clinical advantages not only on grounds of patient acceptability and safety, but also in optimizing image quality for some CT applications. However, ionic media may prove to have advantages for parenchymal imaging. There is a pressing need for further research into the very early comparative pharmacokinetics of contrast media.

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Appendix A

This argument follows the discussion of Burbank [6]. Let MTT be the mean transit time of the bolus, CO be cardiac output, D be the amount of iodine injected, CBV be the central volume, *i.e.* the volume of blood between the injection and sampling site. When the attenuation–time curve is corrected for recirculation and has peak height PH, area AUC and width W, then

$$AUC \approx PH \times W \quad (A1)$$

$$W \approx MTT_c \quad (A2)$$

From the Stuart–Hamilton relationship

$$CO \approx D/AUC = CBV/MTT_c$$

Then by Assumption (A1) $CO \approx D/(PH \times W)$ so

$$CO \approx D/(PH \times MTT_c)$$

by Assumption (A2) and hence

$$PH \approx D/CBV$$

Despite the approximations, Burbank obtained good experimental support for these relationships.

Appendix B

This follows a *reductio ad absurdum* argument. Assume $AUC \approx PH \times MTT_c$ for all gamma variate curves of parameters k, a and b, then, as

$$PH = k(ab/e)^a$$

$$MTT_c = b(a+1)$$

$$AUC = kb^{a+1}\Gamma(a+1)$$

where $\Gamma(x)$ is the gamma function of x.

It follows (rearranging) that

$$\Gamma(a+1) \approx (a+1)a^a/e^a$$

It is easily verified that this is not true for most values of a. (For example recall that $\Gamma(a+1) = a!$ for integer a.)

Appendix C. The two-compartment model

Consider two completely mixed compartments: plasma (compartment 1) and the averaged extracellular space ECF (compartment 2). This is shown diagrammatically (Figure 3). Contrast medium is further assumed slowly to leave the ECF and pass to the urine (compartment 0). Suppose the plasma iodine concentration is $p(t)$ and that of the ECF is $e(t)$. Then, if the rate constant for mass transfer (expressed in terms of net mass exchange) between plasma and ECF is k and that for urinary filtration is θk (where is θ ($\theta < 1$) is a constant reflecting the ratio between renal clearance and whole-body transfer to the ECF) and if V_p and V_s are plasma and ECF volumes respectively

$$V_p \times d/dt[p(t)] = ke(t) - k(1+\theta)p(t)$$

$$V_e \times d/dt[e(t)] = kp(t) - ke(t)$$

It follows from solution of the paired differential equations that

$$e(t) = C(e^{-\beta t} - e^{-\alpha t})$$

$$p(t) = Ae^{-\alpha t} + Be^{-\beta t} \qquad \text{(C1)}$$

where

$$\alpha = k/2[2 + \theta + \sqrt{(4+\theta^2)}] \qquad \text{(C2)}$$

and

$$\beta = k/2[2 + \theta - \sqrt{(4+\theta^2)}]$$

and A, B and C are constants, where $A + B = p(0) = D/V_p$, where D is contrast dosage and V_p is the distribution volume of plasma (so $p(0) \times V_p = D$). The relationship follows from the linearity between plasma iodine concentration and the rise in the CT number.

Appendix D

It follows immediately from Equation (C2) of Appendix C that if renal excretion is slow and θ is relatively small the expression

$$\alpha = k/2\{2 + \theta + 2\sqrt{[1 + (\theta/2)^2]}\}$$

simplifies to

$$\alpha \approx 2k$$

as $\sqrt{(1+x)} \approx 1 + x/2$ for small x.

Appendix E

This appendix analyses the early transit of contrast medium from the vascular space. From Equation (C1) in Appendix C

$$p(t) = Ae^{-\alpha t} + Be^{-\beta t}$$

For small t,

$$e^{-\alpha t} \approx 1 - \alpha t,$$

and

$$e^{-\beta t} \approx 1 \text{ as } \alpha \gg \beta$$

So

$$p(t) \approx A(1 - \alpha t) + B = A + B - A\alpha t$$

So

$$V_p p(t) \approx D - \chi(t)$$

where $\chi(t) = V_p A\alpha t$.

The left hand term $V_p p(t)$ represents the total amount of contrast in the plasma. $\chi(t)$ is thus a measure, to first order in t, of the proportion of the total dose of contrast which has effectively passed to the extravascular space.

It thus follows that if α is reduced by the same approximate factor of λ (for example if α for iohexol is 0.6 and for diatrizoate is 0.8, λ is $0.6/0.8 = 0.75$), then $\chi(t)$ is reduced by the same value λ at early times. It thus follows that losses to the extravascular space for small t are directly proportional to changes in both α and k.