JOURNAL OF MATERIALS SCIENCE: MATERIALS IN MEDICINE 4 (1993) 503–508

Formulation and setting times of some calcium orthophosphate cements: a pilot study

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Calcium orthophosphates which either can be formed by precipitation at room or body temperatures or by reactions at higher temperatures have been reviewed. Most formulations of cements contain at least one or more acidic components and one or more basic components which react when the powder is mixed with water. Several combinations of reactants are possible in the systems of calcium phosphates and even combinations with calcium phosphates containing sodium, potassium, magnesium, zinc, carbonate or chloride are thought to be useful. Furthermore, other compounds can be added as accelerators or retarders of the setting reaction or as promoters of bone ingrowth. In this study, over 100 formulations have been tested on their ability to set upon mixing with water. The initial and final setting times were measured with Gilmore needles.

1. Introduction

The term "calcium phosphate cements" was introduced by Gruninger *et al.* [1]. Such a cement may be described as a powder or a mixture of powders which, upon mixing with water or an aqueous solution to a paste, reacts at around room or body temperature by the formation of a precipitate containing crystals of one or more calcium phosphates, and sets by the entanglement of the crystals of that precipitate. In fact, up to now only orthophosphate cements have been reported in the literature. Brown and Chow [2] were the first to develop a calcium orthophosphate cement. They prepared mixtures of dicalcium phosphate dihydrate (DCPD) with tetracalcium phosphate (TTCP) and of dicalcium phosphate (DCP), TTCP and hydroxyapatite (HA) and reported a lowering of setting times with increasing HA content, from 22 min to 8 min as measured with a Vicat needle. Fukase *et al.* [3] optimised such cements as derived from mixtures of DCP and TTCP. They added some fluoride to the aqueous solution and reported that the reaction product was HA and that the setting reaction was completed within 24 h, when the samples were kept under 100% relative humidity at 37 °C.

Another type of calcium orthophosphate cement has been developed by Lemaitre *et al.* [4]. They found that mixtures of monocalcium phosphate monophydrate (MCPM) and β-tricalcium phosphate (β-TCP) mixed with water to a paste, set at room temperature within 2 min. Mirtchi *et al.* [5] reported that the reaction product in such cements was DCPD. Furthermore, Mirtchi *et al.* [6] measured the setting times of such cements with admixtures of calcium sulphate dihydrate, calcium sulphate hemihydrate and/or calcium pyrophosphate, and found that these admixtures increased the setting time from about 1 up to 10 min, as measured with a Vicat needle.

Hardened products of calcium phosphates were developed by Monma [7], who made pastes of water with mixtures of DCPD and calcium carbonate (Monma did not report which calcium carbonate) or of DCP with calcium carbonate and kept them at 50 or 80 °C for 16–40 h. By X-ray diffraction and infrared spectroscopy they proved that either octocalcium phosphate (OCP) or carbonated hydroxyapatite, or both, were formed, but they did not report any setting times. Earlier, Monma and Kanazawa [8] reported that hardened bodies could be produced by keeping pastes of α-TCP with water at temperatures between 60 and 100 °C. The reaction product was a calcium-deficient apatite with a Ca/P molar ratio near 1.50. These products can hardly be called cements, because the setting temperatures are impracticably high.

A third type of calcium orthophosphate cements was developed by Monma *et al.* [9]. They prepared mixtures of α-TCP with DCPD and added water to form pastes which appear to set within 9–30 min as measured with a Vicat needle. The reaction product in these mixtures was OCP.

Oonishi [10] reported that mixtures of α-TCP with collagen gels or of TTCP with collagen gels could set upon implantation into the bones of animals. However, it is not clear what the reaction products are, so that it is unknown whether these products can be considered as calcium orthophosphate cements.

The development of a fourth calcium orthophosphate cement was reported by Nishimura *et al.* [11]. They prepared a glass from the system CaO–SiO_2–P_2O_5–CaF_2, fractured it and milled it to a particle size of 325 mesh, with an average of 5 μm.

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When mixed with a solution of diammonium hydrogen phosphate into a paste, this paste set in about 6 min at room temperature, measured with a Vicat needle, under the formation of calcium ammonium phosphate monohydrate. Upon immersion of that cement in water, the reaction product was transformed into hydroxyapatite within 1 week.

The purpose of the present study was to develop a more systematic approach for the formulation of calcium orthophosphate cements and to screen the possible combinations of constituents for setting at room temperature after mixing into pastes with water.

2. Materials and methods

Most cement powders consist of an acidic compound and a basic compound which upon mixing with water react to form one or more products with intermediate acidity. Table I lists the solids occurring around room temperature in the system $Ca(OH)_2$–H_3PO_4–H_2O. However, there are many more possibilities to make combinations of acidic and basic compounds. Other calcium phosphates known to form at high temperatures in the system CaO–P_2O_5–H_2O are mentioned in Table II. As the body fluids also contain sodium, potassium, magnesium, zinc carbonate, sulphate and chloride, other inorganic compounds can be used also for the formulation of calcium orthophosphate cements as well as organic compounds such as biopolymers, organic acids, biodegradable synthetic polymers, growth factors, osteocalcine, GLA proteins, etc. Some examples are mentioned in Table III.

In this pilot study, we arranged the calcium phosphates and CaO or $Ca(OH)_2$ in a series of increasing basicity. This order is that dictated by Ca/P ratio:

$$\begin{aligned} \text{MCPM} < \text{DCP} = \text{DCPD} < \text{OCP} < \alpha\text{-TCP} \\ = \beta\text{-TCP} = \text{CDHA} < \text{PHA} \\ = \text{SHA} < \text{TTCP} < \text{CaO} \\ = Ca(OH)_2 \end{aligned}$$

In principle, any of the calcium phosphates (as an acidic component) can be combined with another compound positioned more to the right (as a basic component). But here we find limitations set by the limited number of calcium phosphates which can be

TABLE I Solids occurring in the system $Ca(OH)_2$–H_3PO_4–H_2O around room and body temperature

Ca/P	Formula	Abbreviation	Remarks
0.5	$Ca(H_2PO_4)_2 \cdot H_2O$	MCPM	Stable below pH 2
1	$CaHPO_4 \cdot 2H_2O$	DCPD	Stable between pH 2 and 4, nucleates rapidly and may grow rapidly even up to pH 6.5
1.33	$Ca_8(HPO_4)_2(PO_4)_4 \cdot 5H_2O$	OCP	Nucleates rapidly and grows between pH 6.5 and 8, more stable than DCPD or ACP in that range
1.5	$Ca_3(PO_4)_2 \cdot xH_2O$	ACP	This substance occurs as the first phase when precipitation is done at high concentrations between a pH of 4 and 8, but it transforms rapidly into DCPD, OCP or CDHA. When it incorporates Mg ions, it is stabilized so that it becomes even more stable than CDHA
1.5	$Ca_9(HPO_4)(PO_4)_5OH$	CDHA	This hydroxyapatite is calcium dificient. It does not precipitate spontaneously at room or body temperature but has either DCPD or OCP as precursors. However, it may be in metastable equilibrium with aqueous solutions indefinitely
1.67	$Ca_{10}(PO_4)_6(OH)_2$	PHA	Precipitated hydroxyapatite is the most stable compound in this system at a pH higher than 4. It precipitates directly only above pH 8. However, at lower pH its nucleation can be initiated by fluoride
2.0	$Ca(OH)_2$		This solid is stable only in aqueous solutions not containing any phosphate with a pH higher than about 12

TABLE II Compounds in the system CaO–P_2O_5–H_2O which are stable at higher temperatures

Ca/P	Formula	Abbreviation	Remarks
1.0	$CaHPO_4$	DCP	Formed by precipitation at higher temperatures and is slightly more stable than DCPD
1.5	$Ca_3(PO_4)_2$	β-TCP	Stable up to 1180 °C. In water it is more stable than DCPD or OCP but less than CDHA in the range between pH 6 and 8
1.5	$Ca_3(PO_4)_2$	α-TCP	Forms by heating above 1180 °C and retains its structure when quenched to room temperature. In water it is less stable than DCPD or OCP
1.67	$Ca_{10}(PO_4)_6(OH)_{2-2x}O_x$	SHA	Sintered hydroxyapatite forms by heating between about 700 and 1400 °C. In water it is as stable as CDHA
2.0	$Ca_4(PO_4)_2O$	TTCP	Forms by heating at temperatures above 1500 °C and retain its structure when cooling in the furnace to room temperature. In water it is less stable than SDHA, CDHA, DCPD or OCP
∝	CaO		Forms by heating $CaCO_3$ at temperatures higher than about 450° C

formed by direct precipitation from aqueous solutions at room or body temperature. According to a recent summary [12] the calcium phosphates which can precipitate directly from aqueous solutions and which contain only biocompatible constituents are those mentioned in Table IV (up to now there has been some doubt in the literature about whether CDHA, PCCA, SCCA and HCHA precipitate directly from aqueous solutions or whether they need some precursor phase [12]). Therefore, the compositions of the supposed reaction products in this pilot study were chosen so that they were oriented to result in the formation of one of the compounds mentioned in Table IV.

A second criterion selected for the formulation of the powder mixtures tested in this study is related to the fact that sometimes nucleus formation is difficult, but that growth of nuclei is less of a problem. In order to avoid that problem, in most cases not only the intended reacting compounds but also the most suitable intended seed material was added in many formulations.

In determining the optimum water/powder ratio of the paste, the criterion was used which ratio gave the most suitable consistency at the lowest possible W/P ratio. Although this looks like a very subjective criterion, most technologists in cement technology are used to applying it. We express the W/P ratio in g g^{-1}. The lowest mixing time was kept at 30 s, the highest at 2 min.

The setting times of the pastes obtained in this way were determined at room temperature using not one, but two needles according to the method of Gilmore as mentioned by Phillips [13]. The light needle (113.4 g) with a large diameter (2.13 mm) was used to determine the initial setting time, I, whereas the final setting time, F, was determined by applying the heavy needle (453.6 g) with a small diameter (1.06 mm). The practical value of I is that it reflects more or less the time for which the cement must not be touched before it is set completely, because otherwise the structure which is forming will be destroyed by application of even very small loads. The practical value of F is that touching of the cement is allowable from then on, albeit with much care so as not to destroy its structure. The values of I and F were expressed in minutes as measured from the beginning of mixing.

3. Results

The results are given in Table V. Determination of I was carried out every 2.5 min, that of F every 5 min. The room temperature of the laboratory may have varied from 20 to about 30 °C. The humidity was estimated to have varied between 70% and 95% relative humidity, because the laboratory is located close to the sea.

4. Discussion

This pilot study is not complete in the sense that we did not test all the possibilities which lie within the framework of those indicated in Section 2. For ex-

TABLE III Compounds which might be suitable as accelerators, retarders, additives or reactants in mixtures of calcium orthophosphate cements

Component	Compounds
Sodium	$CaNaPO_4$(α or β), $Ca_{10}Na(PO_4)_7$(α or β), $Ca_{8.5}Na_{1.5}(PO_4)_{4.5}(CO_3)_{2.5}$, NaF, Na_2CO_3, Na_2SO_4, NaCl, orthophosphates of Na
Potassium	$CaKPO_4$, $Ca_9K(PO_4)_5(CO_3)_2$,KF, K_2CO_3, K_2SO_4, KCl, orthophosphates of K
Magnesium	$Ca_4Mg_5(PO_4)_6$, $MgHPO_4$, $Mg_3(PO_4)xH_2O$, MgF_2, $MgCO_3$, MgO, $MgCl_2$, $CaMg(CO_3)_2$, $Mg(OH)_2$, $MgSO_4$
Zinc	$CaZn_2(PO_4)_2$, $Zn_3(PO_4)_2{\cdot}4H_2O$, ZnF_2, $ZnCO_3$, $ZnSO_4$, $ZnCl_2$, ZnO, $Zn(OH)_2$
Calcium	$CaSO_4$, $CaSO_4{\cdot}2H_2O$, $CaSO_4{\cdot}1/2H_2O$, CaF_2, $Ca_{10}(PO_4)_6F_2$, $CaCO_3$, $CaCl_2$, Ca_2PO_4Cl, $Ca_{10}(PO_4)_6Cl_2$
Biopolymers	Proteins, peptides, proteoglycans, glycosaminoglycans, carbohydrates, etc.
Organic acids	Citric acid, malonic acid, pyruvic acid, tartaric acid, etc.
Inorganic acid	Phosphoric acid, etc.
Synthetic polymers	Polylactic acid, polyglycolic acid, etc.
Growth factors	TGF-β, osteocalcine, GLA proteins, etc.

TABLE IV Calcium phosphates which contain only biocompatible constituents and which are thought to be precipitated directly from aqueous solutions [12] around room or body temperature.

Ca/P	Formula	Abbreviation	Name
0.5	$CaZn_2(PO_4)_2$	CZP	Calcium zinc phosphate
1.0	$CaHPO_4{\cdot}2H_2O$	DCPD	Dicalcium phosphate dihydrate
1.28	$Ca_9Mg(PO_4)_6(HPO_4)$	MWH	Magnesium whitlockite
1.33	$Ca_8(HPO_4)_2(PO_4)_4{\cdot}5OH_2$	OCP	Octocalcium phosphate
1.5	$Ca_9(HPO_4)(PO_4)_5OH$	CDHA	Calcium-deficient hydroxyapatite
1.67	$Ca_{10}(PO_4)_6(OH)_2$	PHA	Precipitated hydroxyapatite
1.67	$Ca_{10}(PO_4)_6F_2$	FA	Fluorapatite
1.8	$Ca_{8.5}Na_{1.5}(PO_4)_{4.5}(CO_3)_{2.5}$	SCCA	Sodium and carbonate containing apatite
1.89	$Ca_9K(PO_4)_5(CO_3)_2$	PCCA	Postassium and carbonate containing apatite
2.0	$Ca_9(PO_4)_{4.5}(CO_3)_{1.5}(OH)_{1.5}$	HCHA	Heavily carbonated hydroxyapatite

TABLE V Formulations and their setting times (n = 3)

Sample	Selected reactants	Ca/P ratio of mixture of reactants	Selected seed material	Seed material in cement powder (wt %)	W/P ratio	Initial setting time (min)	Final setting time (min)
1	MCPM,CaO	1.50	PHA	40	0.6	15	30
2	MCPM,CaO	1.67	PHA	40	0.7	8	20
3	DCP,CaO	1.50	PHA	40	0.5	5	30
4	DCPD,CaO	1.50	PHA	40	0.5	10	> 60
5	α-TCP	1.50	PHA	40	0.5	20	60
6	MCPM,CaO,$CaMgO_2$	1.28	β-TCP	40	0.6	5	> 60
7	DCP,CaO,$CaMgO_2$	1.28	β-TCP	40	0.3	5	18
8	DCPD.CaO,$CaMgO_2$	1.28	β-TCP	40	0.35	12	30
9	MCPM,TTCP	1.50	PHA	40	0.7	20	60
10	DCP,TTCP	1.50	PHA	40	0.5	15	50
11	DCP,TTCP	1.50	–	–	0.3	25	45
12	DCP,TTCP	1.67	–	–	0.25	10	25
13	DCPD,TTCP	1.50	PHA	40	0.5	15	50
14	DCPD,TTCP	1.67	–	–	0.25	5	35
15	MCPM,β-TCP	1.00	DCPD	10	0.5	1	2
16	MCPM,β-TCP	1.00	–	–	0.5	1	2
17	MCPM,TTCP	1.00	DCPD	10	0.4	5	10
18	MCPM,$Ca(OH)_2$	1.00	DCPD	10	0.4	10	45
19	DCPD,α-TCP	1.33	–	–	0.35	25	> 60
20	DCPD,α-TCP	1.33	PHA	40	0.55	15	60
21	DCPD,TTCP	1.33	PHA	40	0.55	15	60
22	DCPD,CaO	1.33	PHA	40	0.55	25	> 60
23	DCPD,$Ca(OH)_2$	1.33	PHA	40	0.55	40	> 60
24	MCPM,α-TCP	1.33	PHA	40	0.65	10	60
25	MCPM,TTCP	1.33	PHA	40	0.70	25	> 60
26	MCPM,CaO	1.33	PHA	40	0.75	10	30
27	MCPM,$Ca(OH)_2$	1.33	PHA	40	0.75	20	> 60
28	DCP,α-TCP	1.33	PHA	40	0.50	10	55
29	DCP,TTCP	1.33	PHA	40	0.55	15	50
30	DCP,CaO	1.33	PHA	40	0.55	15	> 60
31	DCP,$Ca(OH)_2$	1.33	PHA	40	0.55	20	> 60
32	MCPM,β-TCP,$CaMgO_2$	1.28	β-TCP	40	0.45	25	> 60
33	DCP,β-TCP,$CaMgO_2$	1.28	β-TCP	40	0.30	15	25
34	DCPD,β-TCP,$CaMgO_2$	1.28	β-TCP	40	0.35	15	> 60
35	MCPM,α-TCP,$CaMgO_2$	1.28	β-TCP	40	0.55	20	55
36	DCP,α-TCP,$CaMgO_2$	1.28	β-TCP	40	0.30	15	30
37	DCPD,α-TCP,$CaMgO_2$	1.28	β-TCP	40	0.35	15	30
38	MCPM,TTCP,$CaMgO_2$	1.28	β-TCP	40	0.55	30	> 60
39	DCP,TTCP,$CaMgO_2$	1.28	β-TCP	40	0.30	20	30
40	DCPD,TTCP,$CaMgO_2$	1.28	β-TCP	40	0.35	20	45
41	MCPM,CaO	1.50	PHA	40	0.70	5	15
42	MCPM,CaO	1.50	SHA	40	0.5	5	25
43	DCP,TTCP	1.50	SHA	40	0.28	10	40
44	OCP,TTCP	1.50	PHA	40	0.6	7.5	60
45	MCPM,α-TCP	1.33	–	–	0.5	35	> 60
46	MCPM,α-TCP	1.33	SHA	40	0.35	20	50
47	MCPM,α-TCP,$CaMgO_2$	1.28	–	–	0.55	12.5	25
48	DCPD,αTCP	1.33	SHA	40	0.35	15	50
49	DCP,α-TCP	1.33	SHA	40	0.35	17.5	45
50	DCP,α-TCP	1.33	–	–	0.30	20	45
51	α-TCP	1.50	SHA	40	0.35	25	> 60
52	OCP,$Ca(OH)_2$	1.50	–	–	0.85	25	> 60
53	MCPM,CaO	1.50	–	–	0.7	8	30
54	DCP,CaO	1.50	–	–	0.35	15	25
55	MCPM,CaO,$CaMgO_2$	1.28	–	–	0.7	10	50
56	DCP,CaO,$CaMgO_2$	1.28	–	–	0.35	20	35
57	DCPD,CaO,$CaMgO_2$	1.28	–	–	0.4	20	45
58	MCPM,TTCP	1.50	–	–	0.50	15	> 60
59	MCPM,TTCP	1.33	–	–	0.50	5	45
60	MCPM,TTCP	1.33	SHA	40	0.50	30	> 60
61	MCPM,CaO	1.33	–	–	0.60	7.5	35
62	MCPM,CaO	1.33	SHA	40	0.50	7.5	30
63	DCP,TTCP	1.33	–	–	0.30	15	25
64	DCP,CaO	1.33	–	–	0.30	7	13
65	DCPD,TTCP	1.33	–	–	0.40	15	55
66	MCPM,β-TCP,$CaMgO_2$	1.28	–	–	0.50	15	50
67	DCP,β-TCP,$CaMgO_2$	1.28	–	–	0.35	20	35
68	DCP,α-TCP,$CaMgO_2$	1.28	–	–	0.40	25	> 60

TABLE V (continued)

Sample	Selected reactants	Ca/P ratio of mixture of reactants	Selected seed material	Seed material in cement powder (wt %)	W/P ratio	Initial setting time (min)	Final setting time (min)
69	SWH,CA	1.50	–	–	0.30	20	50
70	SWH,CA,DCP	1.33	–	–	0.30	30	> 60
71	SWH,CA,DCPD	1.33	–	–	0.35	15	> 60
72	RH,SP	1.50	–	–	0.30	> 60	–
73	RH,SP,DCP	1.33	–	–	0.30	> 60	–
74	RH,SP,DCPD	1.33	–	–	0.35	35	> 60
75	MCPM,CaO,$CaCO_3$	2.00	–	–	0.75	10	25
76	DCP,CaO,$CaCO_3$	2.00	–	–	0.40	7.5	> 60
77	DCPD,CaO,$CaCO_3$	2.00	–	–	0.50	10	> 60
78	$CaKPO_4$,SP,CaO	1.67	–	–	0.30	7.5	55
79	$CaKPO_4$,SP,DCP	1.33	–	–	0.30	35	> 60
80	$CaKPO_4$,SP,DCPD	1.33	–	–	0.35	20	60
81	MCPM,CaO,$CaCO_3$	2.00	HA	40	0.75	7.5	> 60
82	DCP,CaO,$CaCO_3$	2.00	HA	40	0.55	5	50
83	DCPD,CaO,$CaCO_3$	2.00	HA	40	0.55	5	50
84	DCP,$Ca(OH)_2$,$CaCO_3$	2.00	HA	40	0.55	10	60
85	RH,SP	1.50	HA	40	0.50	> 40	–
86	RH,SP,CaO	1.67	HA	40	0.55	27.5	> 60
87	RH,SP,DCP	1.33	HA	40	0.50	> 35	–
88	RH,SP,MCPM	1.33	HA	40	0.50	> 35	–
89	RH,SP,DCPD	1.33	HA	40	0.50	25	> 60
90	MCPM,RH,SP	1.00	DCPD	10	0.30	15	> 60
91	SWH,CA	1.50	HA	40	0.35	20	55
92	RH,CA	1.50	HA	40	0.45	10	> 60
93	SWH,SP	1.50	HA	40	0.45	25	> 60
94	$CaKPO_4$,CA	1.50	HA	40	0.50	40	> 60
95	$CaKPO_4$,SP	1.50	HA	40	0.50	35	> 60
96	$CaKPO_4$,SP,CaO	1.67	HA	40	0.50	12.5	> 60
97	$CaKPO_4$,SP,DCP	1.33	HA	40	0.55	> 40	–
98	$CaKPO_4$,SP,MCPM	1.33	HA	40	0.55	7.5	45
99	$CaKPO_4$,SP,DCPD	1.33	HA	40	0.55	15	35
100	$CaKPO_4$,SP,MCPM	1.00	DCPD	10	0.50	30	> 60
101	MCPM,β-TCP	1.00	–	–	0.40	1.5	2.5
102	MCPM,β-TCP	1.00	DCPD	20	0.40	1.5	3
103	MCPM,β-TCP	1.00	DCPD	30	0.40	2	4
104	MCPM,β-TCP	1.00	DCPD	40	0.40	2	6
105	SWH,CA,DCP	1.33	PHA	40	0.50	15	60
106	SWH,CA,DCPD	1.33	PHA	40	0.50	5	50
107	SWH,CA,MCPM	1.33	PHA	40	0.55	10	> 60
108	SWH,CA,MCPM	1.00	DCPD	40	0.45	4	12.5

ample, instead of CaO or $Ca(OH)_2$, $CaCO_3$ in its three different forms could have been used as a basic compound. Furthermore, instead of α-TCP or β-TCP or CDHA, a combination of spodiosite (SP = Ca_2PO_4Cl) or chloroapatite (CA = $Ca_{10}(PO_4)_6Cl_2$) with either rhenanite (RH = $CaNaPO_4$) or calcium potassium phosphate ($CaKPO_4$) or sodium whitlockite (SWH = $Ca_{10}Na(PO_4)_7$) could have been used (such possibilities were tested only partially). On the other hand, as seed materials, DCPD could have been used in many more formulations than was, in fact, done. The same holds for β-TCP, which is supposed to be a good seed material for MWH. Consequently, the most followed path was that to investigate the value of using PHA as a seed material for the apatite family of CDHA, HA, FA, PCCA, SCCA and HCHA. OCP was used only rarely as a seed material for itself. The good epitaxy of PHA for OCP [14, 15], indicates that tedious approach (OCP is very difficult to make) is not worth trying. Therefore, PHA or SHA was also intended as seed material in cases where the expected reaction product was OCP.

In this phase of the studies it has not yet been checked whether the reaction took place or what was the resulting reaction product. It was thought that determinations of the setting times were the fastest method to determine whether or not something interesting happened in the pastes prepared. The purpose of this study was a quick screening of some possibilities (as many as possible within the time available) to formulate calcium orthophosphate cements. To a first approximation, this study points out that formulations are only suitable for surgery or dentistry when $I > 5$ min. Furthermore it is impractical to have cements for which $F > 60$ min. Therefore, we did not carry out determinations if F was longer than 60 min. Follow-up studies will show whether this approach was right.

Acknowledgements

This study was supported by a grant from the Dirección General de Investigación Científica y Técnica of Spain, and the authors also thank CICYT for funding this work through project MAT89-0277.

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Received 6 April
and accepted 14 September 1992