Circulating excitation in the heart

Citation for published version (APA):

Allessie, M. A. (1977). *Circulating excitation in the heart*. [Doctoral Thesis, Maastricht University]. Rijksuniversiteit Limburg. <https://doi.org/10.26481/dis.19770304ma>

Document status and date:

Published: 01/01/1977

DOI:

[10.26481/dis.19770304ma](https://doi.org/10.26481/dis.19770304ma)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
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Circulating Excitation in the Heart

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van Doctor in
de Geneeskunde aan de Rijksuniversiteit Limburg,
op gezag van de Rector Magnificus Dr. H.A. Tiddens,
Hoogleraar aan de Faculteit der Geneeskunde, volgens besluit
van het College van Dekanen, in het openbaar te ver-
dedigen in de Aula van de Universiteit, Tongerse-
straat 53, Maastricht, op vrijdag 4 maart
1977, des namiddags om 16.00 uur door

Mauritius Antonius ALLESSIE

geboren te Cemert

Maastricht, 1977

Drukkerij RULimburg

Promotores: Dr. F.I.M. Bonke

Prof. Dr. L.N. Bouman

Referenten: Dr. M.J. Janse

Prof. Dr. H.J.J. Wellens

Het in dit proefschrift beschreven onderzoek werd verricht in het Fysiologisch Laboratorium van de Universiteit van Amsterdam. Uitgave werd mede mogelijk gemaakt door financiële steun van de Nederlandse Hartstichting.

Dank-zij PAULA
MARTIJN
MICHIEL

Voorwoord

Het onderzoek, zoals beschreven in dit proefschrift, is niet het werk van één man. De tijd dat een onderzoeker geheel zelfstandig vruchtbaar en grensverleggend onderzoek kon verrichten lijkt, althans voor de biomedische wetenschappen grotendeels voorbij. Verdieping van ons inzicht in de vele facetten van de Geneeskunde kan in de meeste gevallen slechts door langdurige en moeizame arbeid worden bereikt. Vaak is hierbij een multi-disciplinaire benadering vereist. Bovendien worden de voor het onderzoek noodzakelijke technieken steeds ingewikkelder, terwijl de hoeveelheid verkregen meetgegevens hiermee tenminste evenredig toeneemt. Een en ander brengt met zich mee dat biomedisch onderzoek tegenwoordig bijna uitsluitend in groepsverband wordt verricht. De omschrijving van een proefschrift in het Academisch Statuut als zijnde een geschrift dat het resultaat is van onderzoek uitgevoerd door één persoon, dient daarom als een contradictio in terminis te worden beschouwd.

Gaarne wil ik dan ook van deze gelegenheid gebruik maken al diegenen te noemen die direct of indirect hebben bijgedragen tot het tot stand komen van dit proefschrift.

Dit onderzoek is samen met dr. F.I.M. Bonke en mevrouw F.J.G. Wilms-Schopman gedaan. Het is mijn vaste overtuiging dat zonder hun hulp en zonder de hechte teamgeest en onderlinge vriendschap, die sinds vele jaren tussen ons drieën bestaat, dit onderzoek vroegtijdig schipbreuk zou hebben geleden. Niet alleen hebben wij elkaar op een bijna perfecte wijze aangevuld en sterk wederzijds motiveerend gewerkt, maar bovendien is deze samenwerking altijd een bron van grote vreugde voor mij geweest.

Dr. Bonke, beste Vic, vlak voordat jezelf voor een jaar naar het Fysiologisch Laboratorium in Bern vertrok, wist je mij te interesseren voor jouw onderzoek. Als kundig organisator, haalde je me over het fenomeen van de herhaalde ontladingen in de hartspier, waar je toen juist op gestuit was, tijdens jouw afwezigheid te onderzoeken. Dat is het begin geworden van een steeds groeiende samenwerking en een langdurige vriendschap die voor mij van grote betekenis zijn. Het lijkt haast onnodig te zeggen dat ik veel van je heb geleerd. Het vervult me

met grote voldoening je vandaag als promotor te ontmoeten.

Mevrouw F.J.G. Wilms-Schopman, beste Francien. Je hebt dit onderzoek van begin tot einde mede gedragen. Het feit dat je co-auteur bent van de drie publicaties, die de kern vormen van dit proefschrift, is hiervoor reeds voldoende bewijs. Ik ben je zeer veel dank verschuldigd voor het vele werk dat je in het kader van dit onderzoek hebt gedaan en met name voor de plezierige sfeer waarin we altijd hebben samengewerkt.

Prof. dr. L.N. Bouman, geachte promotor. Jij hebt in het Fysiologisch Laboratorium van de Universiteit van Amsterdam de hartgroep opgericht die de voedingsbodem is geweest waarop het onderzoek, dat de basis vormt van dit proefschrift, is gegroeid. Ook persoonlijk ben je van grote invloed geweest op mijn academische vorming. Vaak ben ik onder de indruk gekomen van je grote draagkracht en brillante geest. Jouw grote interesse en verantwoordelijkheidsbesef voor het onderwijs hebben aanstekelijk op mij gewerkt. Jij was natuurlijk ook degene die voorstelde deze promotie in Maastricht te laten plaatsvinden; dit ondanks het feit dat het proefschrift bijna geheel in Amsterdam is bewerkt. Het is tekenend voor je wens anderen van jouw inspanningen te laten profiteren.

Dr. M.J. Janse en Prof. Dr. H.J.J. Wellens wil ik danken voor hun bereidwilligheid om als referenten op te treden. Eerstgenoemde ben ik bovendien veel dank verschuldigd voor de wijze waarop hij tezamen met Drs. F.J.L. van Capelle mij heeft ingewijd in de geheimen van de door hen ontwikkelde 10-voudige microelektrode "borstel".

Prof. dr. Th.F. Boeles. U was, als voorzitter van de vakgroep Fysiologie waar binnen dit proefschrift tot stand is gekomen, de "stille kracht" op de achtergrond, die met volstrekt voorbijgaan aan eigenbelang, voor eenieder altijd het beste heeft nagestreefd. De gunstige omstandigheden waaronder ik dit onderzoek heb kunnen doen, zijn voor een groot deel door u gecreëerd.

Dr. T. Blangé, beste Tuug. Je gewoonte om langzaam te spreken en lang na te denken is ook voor dit proefschrift van grote waarde gebleken. De grondgedachte van het "leading circle" model is tijdens discussies met jou ontstaan.

Andere leden van de hartgroep. De werkbesprekingen die we gedurende vele jaren wekelijks hebben gehouden, zijn voor mij van groot nut geweest. De gedetailleerde kritiek die ik daar heb mogen ondervinden, en de vaak heftige discussies, die daar werden gevoerd, hebben me steeds gedwongen de verkregen resultaten kritisch te bezien en objectief te beoordelen.

Mej. C.E. Besselen, beste Elly. Je hebt de moeilijke opgave om na het vertrek van Francien haar plaats in te nemen, op bewonderenswaardige wijze vervuld. Met name je grote zorg voor een voortdurende aanvoer en distributie van het "Vakmanschap is Meesterschap" belovende elixir, heb ik altijd als een grote wel-daad ondervonden.

De medewerkers van de electronische werkplaats (hoofd: A.A. Meyer) en de mechanische werkplaats (hoofd: A.W. Schreurs) ben ik veel dank verschuldigd voor de ontwikkeling van de nieuwe apparatuur die dit onderzoek mogelijk heeft gemaakt. Ook ben ik dankbaar voor hun onuitputtelijke geduld en begrip waarmee zij, nadat ik door onoordeelkundig gebruik de veelal delicate apparatuur geheel had ontregeld, de ontstane schade in korte tijd weer wisten te repareren.

Bebby van der Mars en Els Geurts hebben het meeste type-werk verricht. De opgewektheid waarmee zij tot het laatste moment de noodzakelijke veranderingen in het manuscript hebben aangebracht was voor mij een grote steun.

Verder wil ik danken: de heer H. Louwès, die zeer nauwgezet het fotografisch werk heeft verricht, de heren B.M. Hilgersom, M. Free en J. Riepen, op wie ik nooit tevergeefs een beroep heb gedaan, de heer J. Alkema en medewerkers voor de verzorging van de proefdieren, de medewerkers van de bibliotheek van het Jan Swammerdam Instituut en van de Rijksuniversiteit Limburg die mij behulpzaam zijn geweest bij het verzamelen van de soms moeilijk te achterhalen literatuur, de heer C. Voskamp voor het ontwerp van de omslag, en de heer J. Meerstad voor de verzorging van het drukwerk.

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The figures of Chapter 1 and 2 are reproduced with permission from the following works and journals:

Circulation Research (figs. 1 and 2 of Chapter 1, and figs. 19, 20, 21, 22, 23, 27, 28, 29, 30, 31, 32, 33, and 34 of Chapter 2), Zeitschrift für Rationelle Medizin (fig. 1 of Chapter 2), Transactions Royal Society of Canada (figs. 2 and 7 of Chapter 2), Carnegie Institution of Washington (fig. 3), Marine Biological Laboratory at Tortugas (figs. 4 and 5), Journal of Physiology (figs. 6 and 8), British Medical Journal (fig. 9; the photograph of Mines was kindly provided by Prof. D.A. Rytand), Heart (figs. 10, 11, and 12), The Tohoku Journal of Experimental Medicine (figs. 13 and 16), The Mechanism and Graphic Registration of the Heart Beat, by T. Lewis, Shaw and Sons, London (fig. 14), American Heart Journal (fig. 15), American Journal of Physiology (figs. 17 and 18), Reentrant Arrhythmias, Mechanisms and Treatment, editor H.E. Kulbertus (figs. 24 and 25), European Journal of Cardiology (fig. 26), De atrium extrasystole, Thesis, by F.I.M. Bonke, Hollandia offset, 1968 (fig. 35).

Part of the present thesis has already been published:

CHAPTER III: Allessie, M.A., Bonke, F.I.M., Schopman, F.J.G.:

Circus movement in rabbit atrial muscle as a mechanism of tachycardia. Circ. Res. 33, 54-62, 1973

CHAPTER IV : Allessie, M.A., Bonke, F.I.M., Schopman, F.J.G.:

Circus movement in rabbit atrial muscle as a mechanism of tachycardia. II. The role of nonuniform recovery of excitability in the occurrence of unidirectional block, as studied with multiple microelectrode. Circ. Res. 39, 168-177, 1976

CHAPTER V : Allessie, M.A., Bonke, F.I.M., Schopman, F.J.G.:

Circus movement in rabbit atrial muscle as a mechanism of tachycardia. III. The "leading circle" concept: a new model of circus movement in cardiac tissue without the involvement of an anatomical obstacle. Circ. Res. 40, 000-000, 1977

Appendix I : Schreurs, A.W., Meyer, A.A., Bouman, L.N., Bonke, F.I.M.:

Micromanipulator with an electrode driver used for microelectrode work. Pfluegers Arch. 346, 163-166, 1974

Appendix II: Schreurs, A.W., Selij, A.P.L., Allessie, M.A., Bonke, F.I.M.:

A concentrically and radially adjustable holder for ten microelectrodes. Pfluegers Arch. 346, 167-170, 1974

Korte Inhoud

Dit hele proefschrift draait om een verschijnsel, cirkelgeleiding of re-entry genaamd. Hiermee wordt de situatie aangeduid dat de elektrische impuls die het startsignaal voor de hartslag is, ergens in het hart in een vicieuze cirkelgang "gevangen" is. Onder normale omstandigheden, waarin het hart met bij voorbeeld 60 slagen per minuut klopt, wordt er elke seconde door een groepje gespecialiseerde hartcellen (de sinusknoop) een zwak elektrisch stroompje gegenereerd. Dit elektrische stroompje breidt zich snel naar alle kanten over het hele hart uit, om tenslotte, zodra de grenzen van het hart bereikt zijn, weer uit te doven. Op deze manier worden alle hartspiercellen kort na elkaar geactiveerd met als gevolg dat het hart zich samentrekt.

Er kunnen zich echter ook stoornissen in dit normale ritme voordoen. Het hart kan bij voorbeeld plotseling zonder schijnbare reden, veel te snel gaan kloppen. Men spreekt dan van een tachycardie. Ook is het mogelijk dat de hartcellen niet alleen in een hoog tempo geactiveerd worden, maar dat tevens de synchronisatie tussen de cellen verloren is gegaan (fibrilleren). Hoewel hierbij iedere cel afzonderlijk een hoge activiteit vertoont, staat het hart dan als geheel stil en wordt er geen bloed meer uitgepompt. Het is mogelijk dat in beide gevallen cirkelgeleiding een belangrijke rol speelt. In plaats van aan de grenzen van het hart uit te doven, wordt de impuls in een cirkelpad gevangen waarin het in principe eindeloos kan blijven rondcirkelen. De hartfrequentie wordt dan niet meer bepaald door de ontlaadingsfrequentie van de sinusknoop, maar door de tijd die de impuls nodig heeft dit cirkelpad één keer te doorlopen. Aangezien in het algemeen deze omlooptijd veel korter is dan de normale pauze tussen twee hartslagen, is het hoge ritme van het hart hiermee verklaard.

In hoofdstuk 2 wordt een overzicht gegeven van de onderzoeken welke door anderen in de loop der tijd over het fenomeen van de cirkelgeleiding zijn gedaan. In hoofdstuk 3, 4 en 5 wordt het eigen onderzoek beschreven, waarin is getracht cirkelgeleiding in de hartspier rechtstreeks aan te tonen. Het bleek mogelijk in een geïsoleerd stukje van de linker hartboezem van het konijn, door het opwekken van één enkele goed geplaatste extra hartslag (extrasystole), experimenteel periodes van tachycardie te veroorzaken. Door op zeer veel plaatsen in dit preparaat de elektrische activiteit te meten, kon het elektrische activatiepatroon van de hartspier nauwkeurig in kaart worden gebracht. Hierbij werd gevonden dat tijdens het langzame, normale ritme de impuls zich naar alle kanten uitbreidde; een der-

gelijk radiaal activatiepatroon is te vergelijken met de golffronten die ontstaan als we een steen in het water gooien. Tijdens de aanval van tachycardie daarentegen was van zulk een radiaire voortgeleiding geen sprake meer. Duidelijk kon worden aangetoond dat in plaats daarvan de impuls in een klein gedeelte van de hartspier rondcirkelde. De verkregen activatiepatronen tijdens tachycardie vertoonden veel gelijkenis met de bewegingen in een draaikolk (zie bij voorbeeld de kaart zoals weergegeven op de omslag).

Deze cirkelgeleiding komt tot stand doordat de extrasystole op een zodanige plaats en op een dusdanig moment ontstaat of wordt opgewekt, dat de impuls van deze extrasystole niet normaal over het hart kan worden voortgeleid; de voortgeleiding is in één richting geblokkeerd (uni-directioneel blok). Wanneer de elektrische impuls zich vervolgens zodanig in het hart voortplant dat via een omweg dit blokgebied alsnog geactiveerd wordt, dan is het mogelijk dat het gebied waar de impuls is ontstaan voor een tweede keer van de andere kant af tot ontlading wordt gebracht (re-entry). Hiermee heeft de impuls een volledige cirkel afgeleid en kan onder bepaalde omstandigheden in dit cirkelpad blijven ronddraaien. Uit ons onderzoek is komen vast te staan dat ook in een betrekkelijk klein gebied ($+ 30 \text{ mm}^2$) van de hartspier cirkelgeleiding kan optreden.

Vervolgens is in hoofdstuk 4 nagegaan welke rol de refractaire periode speelt bij het ontstaan van een dergelijke cirkelgeleiding. Een belangrijke eigenschap van hartcellen is, dat zij, na iedere activatie, enige tijd niet opnieuw geprikkeld kunnen worden. De tijd, die de cellen nodig hebben om hun prikkelbaarheid weer te herstellen (refractaire periode), is niet overal in het hart precies gelijk. Om te onderzoeken of er een causaal verband bestaat tussen deze locale verschillen en het optreden van cirkelgeleiding, werden ook de refractaire periodes in kaart gebracht. Op deze manier kon de wijze van ontstaan van cirkelgeleiding worden vergeleken met de verdeling van de refractaire periodes over de hartspier. Uit deze experimenten bleek dat uni-directionele geleiding - een eerste voorwaarde voor het ontstaan van cirkelbeweging - reeds kon optreden ten gevolge van relatief kleine plaatselijke verschillen in refractaire periode. Indien op de grens van twee gebieden met een verschillende refractaire periode een vroege extrasystole wordt opgewekt, wordt de impuls uitsluitend voortgeleid in de richting waarin de refractaire periode kort is. In andere richtingen, waar de refractaire periode van langere duur is, wordt de geleiding van de impuls geblokkeerd, omdat op het moment dat de extrasystole optreedt, de prikkelbaarheid ter plaatse nog niet vol-

doende hersteld is.

In hoofdstuk 5 tenslotte wordt beschreven wat er gebeurt in het centrum van de cirkelgeleiding. Met behulp van microelectrodes werd het gedrag van individuele cellen in het "oog" van de cirkeltachycardie onderzocht. Met name door de resultaten van deze laatste experimenten kon een model worden opgesteld dat cirkelgeleiding in de hartspier beschrijft zonder dat hierbij een depreformeerd (anatomisch bepaald) pad is betrokken. Met dit model kan het gedrag van dergelijke cirkeltachycardieën onder een groot aantal omstandigheden worden voorspeld. Dit schept de mogelijkheid tachycardieën, zoals die bij patienten voorkomen, te vergelijken met de in dit proefschrift beschreven cirkeltachycardie.

Chapter 1

Introduction

Some years ago, shortly after I entered the Department of Physiology of the University of Amsterdam, for purpose of introduction, I was invited to attend an experiment carried out by Dr. Bonke and Bouman. At that time they were involved in a study on the effect of early premature beats on the normal rhythm of the sino-atrial node. Using the spontaneously beating isolated right atrium of the rabbit, they had sometimes observed that the induction of an early premature stimulus, instead of being followed by a single premature beat, evoked one or more non-stimulated extra beats. In the figure below, which is taken from their publication (BONKE, BOUMAN and SCHOPMAN, 1971), an example of this phenomenon is given.

FIGURE 1. Recording of a spontaneously beating right atrium of the rabbit. Upper trace: electrogram. Middle and lower traces: action potentials of two impaled fibers of the sinoatrial node. In the right part of the figure the intervals between the various beats are given together with the conduction times between the three recording sites. At 80 msec after the last spontaneous electrogram a stimulus was applied to the atrium. This single stimulus, given shortly after the refractory period of the atrium, was followed by two atrial discharges with an interval of 98 and 134 msec respectively. Except for a small electrotonic hump in fiber A, the early premature beat failed to excite the impaled fibers

A reentrant mechanism in the sinus node was considered to be the most likely mechanism underlying these rapid spontaneous discharges. A little earlier HAN, MALOZZI and MOE (1968) had provided evidence for this hypothesis. However, the possibility that the extra non-stimulated beats did not originate in the sinus node, but instead were generated in the atrial myocardium, could not be ruled out completely. The experiment for which I was invited was designed to test this matter. The idea was to repeat the experiment in isolated segments of the *left* atrium. Such an experiment was expected to yield negative results, since it was considered rather unlikely that in the absence of the sinus node, a small piece of ordinary atrial muscle, which normally did not show any tendency of spontaneous activity, would start to generate impulses merely because of the induction of a single premature beat.

However, it turned out to be completely different. Even in a very small piece of ordinary atrial muscle the induction of a single stimulus of short duration and physiological strength (1 msec and $4 \times$ threshold, respectively) indeed could be the trigger for rapid repetitive activity. In figure 2 the original tracings as published by BONKE, BOUMAN and SCHOPMAN in their 1971 paper are reproduced.

FIGURE 2. Recordings of a left atrial preparation of the rabbit. Upper trace: surface electrogram. Lower trace: transmembrane potential. White arrows indicate the basic stimuli and the black arrow indicate the extra stimulus. In A the extra stimulus is followed by a series of 15 repeated atrial discharges; in B the premature beat is followed by only one atrial discharge. Calibration was 50 mv and 1000 msec.

This fortuitous observation which, as appeared later had already been described in a more general way (WEST and LANDA, 1962), was the starting point of this thesis. Initially the question was relatively simple: was this abnormal impulse formation or a reentrant mechanism? In chapter 3, I describe the way we tackled this problem and how we were able to demonstrate that the paroxysms of tachycardia were caused by a circus movement of the impulse. In chapter 4 detailed information is given about the phenomena occurring at the time of initiation of tachycardia. These data were acquired by combining multiple microelectrode recordings and measurements of local refractory periods. In this way it could be ascertained that spatial differences in refractory periods were responsible for the occurrence of unidirectional block during the propagation of the premature beat. In the last chapter of this thesis (chapter 5), a new model of circulating excitation is presented, in which a central anatomic obstacle - essential for most other models of circus movement - is no longer required. This "leading circle" concept is based on intracellular and extracellular measurements from the center of the circulating activation wave. With this model the behaviour of circus movement tachycardia can be predicted under various circumstances. Preceding these chapters, describing our own experimental work, chapter 2 reviews the studies by others, who have largely contributed to our present understanding of circulating excitation in the heart. This review does not pretend to be complete. It reflects my personal view on the history of circus movement in the heart.

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Chapter 2

The memory of the medical profession is short. One uses the knowledge or the remedies with thankfulness and neglects to enquire how they were obtained.

Arthur R. Cushman (1911)

THE HISTORY OF CIRCULATING EXCITATION IN THE HEART

Early description of flutter and fibrillation

It is likely that the phenomenon of a fibrillating heart was rather familiar already to primitive mankind, as there must have been ample opportunity to observe this arrhythmia directly from the dying heart in slaughtered animals. However, it was not until the seventeenth century that the first written report of what might have been atrial flutter or fibrillation appeared. In his famous "Exercitatio anatomica de motu cordis et sanguinis in animalibus", WILLIAM HARVEY wrote in 1628: "But I have also from time to time noticed that, after the heart proper and even its right auricle were ceasing to beat and appeared on the point of death, an obscure movement/undulation/palpitation had clearly continued in the right auricular blood itself". About the exact nature of this arrhythmia one can only speculate, particularly because HARVEY added: "Indeed, one may wonder if the blood or spirit earlier has that obscure throbbing within it which I thought it continued to have after death, and if we may say that life begins with that throbbing".

A more clear description of what now is known as ventricular fibrillation is given by ERICHSEN in 1842, describing "tremulous motion" and "tumultuous" action of the heart following ligation of coronary arteries in the dog.

Systematic experimental production and registration of ventricular fibrillation were introduced by HOFFA and LUDWIG in 1850. They found that the application of strong faradic current to the ventricles of the dog and the rabbit, invariably resulted in fibrillation. "Wenn eine sehr kräftige elektrische Wirkung ein recht reizbares Herz trifft..... gerät das Herz in ausserordentlich rasche, ganz unregelmässige Bewegungen von sehr geringer Intensität. Die Unregelmässigkeit dieser Bewegungen entsteht dadurch, dass die einzelnen anatomischen Elemente sich aus ihren Beziehungen zu einander lösen und die Gleichzeitigkeit ihrer Kon-

traktion aufgeben; hierdurch erzeugt sich in Beziehung auf Rhythmus und Intensität ein Wirrwar, wie Ihnen annähernd Fig. 19 (see Fig. 1 of this chapter) veranschaulicht, welche von einem Kaninchenherzen selbst gezeichnet ist. Um einen ungefähren Begriff von der Beschleunigung der Bewegung zu geben, erwähnen wir das hier beigegebene Kurvenstück, welches 8,34 Sekunden umfasst, 84 Schläge enthält, so dass auf die Minute 604 Herzschläge kommen würden.... Diese Bewegungen überdauern immer den Reiz, und zwar um so länger je anhaltender er eingewirkt hatte". Figure 1 shows the lever system they used for registration of the mechanical activity of the heart together with their first record of ventricular fibrillation.

FIGURE 1. Original drawing of apparatus for direct recording of mechanical activity of the heart as used by Hoffa and Ludwig (1850). In the lower right-hand corner the first graphic registration of ventricular fibrillation is shown. The curve, which is taken from a rabbit heart, represents 8,34 seconds. Fibrillation was induced by strong faradic stimulation.

From this time on the condition in question was studied by various investigators and in 1889 McWILLIAM summarizes its general characteristics as follows: "The normal beat is at once abolished, and the ventricles are thrown into a tumultuous state of quick, irregular, twitching action; at the same time there is a great fall in blood pressure. The ventricles become distended with blood, as the rapid quivering movements of their walls is wholly insufficient to expel their contents. The muscular action partakes of the nature of an arrhythmic, incoordinated and rapidly-repeated contraction of the various muscular bundles. Some bundles are in a

state of contraction while other bundles are relaxed, and so, instead of a co-ordinated contraction leading to a definite narrowing of the ventricular cavity, there occurs an irregular and complicated arrhythmic oscillation of the ventricular walls which remain in a position of diastole. This condition is very persistent, and it is easy to kill a dog by applying a faradic current to the ventricles... The cardiac pump is thrown out of gear, and the last of its vital energy is dissipated in a violent and prolonged turmoil of fruitless activity in the ventricular walls". It is amazing to realize that this early description and explanation of what in that time was designated by various names as Herz delirium, Delirium cordis, Fibrillar contraction, Intervermiform movement, Frémissement fibrillaire, etc., is not far from what we know today about the mechanism of fibrillation. It illustrates our inability to analyze such a complex phenomenon.

After fibrillation of the atria was described by VULPIAN in 1874, some years later McWILLIAM (1887) compared the effects of faradic stimulation of the ventricles and the atria. He found that, in the auricles, faradic stimulation caused atrial flutter rather than fibrillation, a difference which he explained by the simpler architecture of the atria: "The application of the current sets the auricles into a rapid flutter, the rapidity of which largely depends upon the excitability of the auricular tissue and the strength of current employed. The movements are regular; they seem to consist of a series of contractions originating in the stimulated area and thence spreading over the rest of the tissue. The movement does not show any distinct sign of incoordination; it looks like a rapid series of contraction waves passing over the auricular walls. The difference between this appearance and that seen in the ventricles probably depends on the simpler structure and arrangements obtaining in the auricles". He also noticed that the phenomenon of fibrillar contraction is much more readily induced and much more persistent in the higher mammals than in the lower forms (McWILLIAM, 1889).

GARREY (1914) correlated this difference between hearts of different species with the size and the form of the tissues involved. He concluded: "The ease with which the fibrillary contractions take place is inversely proportional to the mass of fibrillating tissue.....fibrillary contractions are not dependent upon impulses initiated in any given area, even if the area be the one from which the process was started, but is a process in which the whole tissue mass

is involved. It is dependent upon the integrity of a considerable mass of tissue, and subdivision of this mass into smaller bits brings all of the tissue out of the state of incoordinated contractions, the pieces either coming to rest or beating independently with a perfect rhythm".

In the same year MINES (1914) discovered that not only faradic stimulation of the heart can induce fibrillation, but that under some conditions a single stimulus of very brief duration, given shortly after the end of the refractory phase, may already be sufficient to induce fibrillation, suggesting that fibrillation may be started by a single ventricular extrasystole of intrinsic origin. "It was found that a single tap of the Morse key *if properly timed* would start fibrillation which would persist for a time which varied in different cases.... the point of interest is that the stimulus employed would never cause fibrillation unless it was set at a certain critical instant". Figure 2 illustrates this phenomenon. In panel A the first stimulus (indicated by a white dot superimposed on the tracing) falls within the refractory phase and does not influence the rhythm. The next stimulus, coming a little later in the cycle, set up fibrillation which persists for a certain length of time and then suddenly ceases. In panel B it is seen that stimuli coming later than the critical moment needed for the production of fibrillation merely induce extrasystoles. Comparison of the effect of the first and the last stimulus indicates that the critical moment for the production of fibrillation is immediately after the end of the refractory phase.

FIGURE 2. Two kymograph tracings, recorded by Mines (1914), which demonstrate that the application of a single stimulus to the apex of a rabbit heart, if properly timed, can induce fibrillation. See text for further explanation

Focal impulse formation versus circulating excitation wave

Over the years, two alternative hypotheses have been developed for the explanation of tachycardia and fibrillation: (1) Abnormal (enhanced) impulse formation, (2) Circus movement of the impulse. For many years there has been an intense discussion between groups of investigators, each advocating one of both theories. Without any justification it was thought that the two concepts were mutually exclusive. Now there is evidence that each of the two hypotheses has its own right. In fact, there are relatively few arrhythmias occurring in man where the cardiologist of today can decide with certainty which mechanism is involved. This lack of knowledge about the properties and behaviour of the underlying mechanisms is the main reason that the prevention and treatment of clinical arrhythmias is still largely based on empirical grounds.

In this review I shall confine myself to those studies which give direct arguments in favour of the circus movement hypothesis. However, I want to emphasize that this should not be considered as argument against the alternative hypothesis of enhanced automaticity. It will greatly depend on the experimental circumstances or clinical conditions which mechanism is involved.

The concept of circulating excitation

The first, rather premature thoughts about a reentrant mechanism as the cause of tachycardia and fibrillation can be found in an article by McWILLIAM published in 1887. There, as an alternative for the earlier proposed possibility of enhanced automaticity he wrote: "For apart from the possibility of rapid spontaneous discharges of energy by the muscular fibers, there seems to be another probable cause of continued and rapid movement. The peristaltic contraction travelling along such a structure as that of the ventricular wall must reach adjacent muscle bundles at different points of time, and since these bundles are connected with one another by anastomosing branches the contraction would naturally be propagated from one contracting fiber to another over which the contraction wave had already passed.....Hence the movement would tend to go on until the excitability of the muscular tissue had been lowered, so that it failed to respond with a rapid series of contractions".

However, with these ideas McWILLIAM was far ahead of his time, and consequently

this early concept of circulating excitation found no echo among other contemporary investigators. Rediscovery of the idea of a circulating impulse came from a rather unexpected side. It was the biologist MAYER, studying the nature of rhythmical pulsation of the jelly-fish, who re-aroused the interest for this phenomenon. In 1906 he found that a strip of paralyzed subumbrella tissue of *Scyphomedusa* cut in the shape of a ring, or closed circuit, will pulsate rhythmically again, provided a contraction-wave be once started in the circuit.

FIGURE 3. Left: views of the jelly-fish *Cassiopea Xamachana* in three stages of preparation. Plate 1: aboral view of the intact animal as it can be found in the moat of Fort Jefferson, Tortugas, Florida. 2. Oral view of subumbrella with stomach and mouth-arms removed. 3. Ring of subumbrella tissue made by cutting off the marginal sense-organs and removing the center of the disk.

Right: apparatus, used by Mayer (1906) to convert a disk of *Cassiopea* (see plate 2) into insulated circuits of tissue. With this apparatus it was no longer necessary to make a series of concentric, discontinuous ring-like cuts through the muscular tissue of the subumbrella. By pressing the concentric series of metallic rings lightly upon the subumbrella, transmission of contraction waves across the pressed region was prevented and isolated circuits were formed. Then upon stimulating the disk in any manner, by a touch of some potassium or sodium salt, or by mechanical or electrical shock, it started to pulsate rhythmically.

"If we cut off the marginal sense-organs of the *Scyphomedusa Cassiopea*, the disk becomes paralyzed and does not pulsate in sea-water. The disk will pulsate in sea-water, however, if we make either a single ring or a series of concentric

broken-ring-like cuts through the muscular tissue of the subumbrella. Then upon momentarily stimulating the disk in any manner, it suddenly springs into rapid, rhythmical pulsation so regular and sustained as to recall the movement of clock-work". Figure 3 shows the jelly-fish and the ring of subumbrella tissue together with the apparatus, consisting of a concentric series of metallic rings, which he used to form circuits by pressing lightly upon the subumbrella. In 1908 MAYER demonstrated that the above described rhythmical activity was due to a single contraction-wave which continuously circulated around the ring. "This single wave going constantly in one direction around the circuit may maintain itself for days travelling at a uniform rate. The circuit must, however, be long enough to allow each point to rest for an appreciable interval of time before the return of the wave. The wave is actually "trapped" in the circuit and must constantly drive onward through the tissue. The point which was stimulated and from which the contraction-wave first arises is of no more importance in maintaining the rhythmical movement than is any other point of the ring....the wave is *not* reinforced and sent forth anew every time it returns to its place of origin, but is maintained by each and every part of the ring in succession as it passes". The latter statement he proved by insulating the point where the wave was originated from the rest of the ring. This intervention did not result in termination of the circus movement but on the contrary the wave continued unhindered through the circuit (see Fig. 4).

FIGURE 4. Showing non-importance of any definitely localized center in maintaining rhythmical pulsation (Mayer, 1908). The point of stimulation where the entrapped circuit was initiated is indicated by S. In panels A-C a single broad ring is divided by two annular cuts into three separate rings. Yet the two inner circles which are completely isolated from the point S remain in sustained pulsation. In panels J, K and L multiple incisions are made in such a way that two independent pulsating circuits are obtained. Since the point of stimulation can only be in one of these circuits it is evident that it plays no essential role in the maintenance of circulating excitation.

With respect to the mechanism of initiation of circus movement, however, MAYER still had erroneous ideas. He stated that, commonly, the waves which arise from the stimulated point are *unequal*, one being strong and the other weak. When the "strong" contraction wave meets the "weak" one at 180° from their common point of origin, he believed that the strong wave would be capable of stimulating the tissue over which the weak wave has just travelled. In figure 5 the diagrams are shown which MAYER used to illustrate this wrong concept.

—Annulment of pulsation which occurs when two waves of equal magnitude, coming in opposite directions, meet each other.

FIGURE 5. Diagrams drawn by Mayer (1908) illustrating his erroneous ideas about the initiation of circus movement in rings of subumbrella tissue of scyphomedusa. Note that the concept of uni-directional block is still missing, and that instead he thought that a "strong" wave, when it meets a "weak" one, is capable of stimulating the tissue over which the weak wave had already travelled.

—Showing that when a strong wave meets a weak one it suppresses the weak wave, and remains the only wave in the circuit.

It seems questionable whether MAYER himself was aware of the utmost importance of his observations with respect to cardiac arrhythmias. Although he repeated his experiments on ring-shaped strips of turtle's ventricle, in which he found the same phenomena as in the rings of medusa, he emphasized: "It is remarkable that these isolated circuit-waves, moving constantly in one direction through a circuit, are *not met with* in nature. Indeed, the heart, or pulsating medusa, contains within itself the means to *prevent* any single pulsation-wave from coursing constantly in one direction through the tissue.... Such a circuit cannot take possession of the vertebrate heart". Fortunately, in contrast to the time of McWILLIAM, there were now two contemporary physiologists who immediately understood the fundamental significance of MAYER's observations in respect to cardiac arrhythmias.

MINES and GARREY, inspired by MAYER's results with the rings of jelly-fish, published a number of important papers at about the same time and independently

of each other. In these articles they made several speculations, predicting the crucial role of circus movement in some cases of paroxysmal tachycardia and fibrillation, as observed clinically in man. MINES (1913) first observed a type of rhythm in auricle-ventricle preparations of the heart of the electric ray and the tortoise (Fig. 6), which he designated as reciprocating rhythm. "The appearance of the heart gave the impression that the beats of the ventricle were caused by those of the auricle, while these in turn were caused by the ventricle. This was confirmed by observation of the effect of sending in a single shock either to the auricle or to the ventricle. This, if timed properly, instantly arrested both chambers. It seems then that the reciprocating rhythm may reasonably be regarded as due to a circulating excitation".

FIGURE 6. Auricle-ventricle preparation of the tortoise in which Mines observed "reciprocating rhythm". The preparation was obtained by making longitudinal incisions extending through the anterior and posterior walls of the heart. Both connections between auricle and ventricle could transmit an excitation wave. During reciprocating rhythm the four portions of the preparation marked V_1 , V_2 , A_1 and A_2 contracted in that order.

MINES as well as GARREY emphasized the fact that for a circulating wave a uni-directional block is a necessary condition. In his explanation of the mode of onset of reciprocating rhythm, MINES considers the existence of spatial differences in refractory periods to be responsible for the occurrence of local block: "A slight difference in the rate of recovery of two divisions of the A-V connection might determine that an extrasystole of the ventricle, provoked by a stimulus applied to the ventricle shortly after activity of the A-V connection, should spread up to the auricle by that part of the A-V connection having the quicker recovery process and not by the other part. In such a case, when the auricle became excited by this impulse, the other portion of the A-V connection would be

ready to take up the transmission again back to the ventricle. Provided the transmission in each direction was slow, the chamber at either end would be ready to respond (its refractory phase being short) and thus the condition once established would tend to continue, unless upset by the interpolation of a premature systole". MINES seemed to be very convinced that these results, obtained from cold-blooded hearts, also hold true for the human heart. In his 1913 paper he predicts: "I venture to suggest that a circulating excitation of this type may be responsible for some cases of paroxysmal tachycardia as observed clinically". Already within one year, after KENT (1913) described a human heart with an extensive muscular connection at the right-hand margin of the junction between the right auricle and the right ventricle, MINES, in his 1914 paper could not refrain from repeating this view: "I now repeat this suggestion in the light of the new histological demonstration by Stanley Kent that the muscular connection between auricles and ventricles in the human heart is multiple. Suppose that for some reason an impulse from the auricle reached the main A-V bundle but failed to reach this "right lateral" connection. It is possible then that the ventricle would excite the ventricular end of this lateral connection, not finding it refractory as normally it would at such a time. The wave spreading then to the auricle, might be expected to circulate around the path indicated". Later analysis of the mechanism of paroxysmal tachycardia in patients with the Wolff-Parkinson-White syndrome indeed has completely confirmed this prediction (see for a review Durrer and Wellens, 1974).

MINES repeated his observations on ring preparations cut from auricles of ray and dogfish and from ventricles of the dog and the cat (see Fig. 7), in which he essentially got the same results. Fig. 8 gives a reproduction of the original diagrams in which MINES summarized his ideas on circus movement. "No fact is better established concerning the histological structure of cardiac muscle than that there exist numerous connections between the various portions or columns of cells. There exist closed CIRCUITS in the myocardium. Supposing an excitation to be started in such a closed circuit and supposing that for some reason it travels in one direction but not in the other. If the rate of propagation is rapid as compared with the duration of the wave, the whole circuit will be in the excited state at the same time, and the excitation will die out (see Fig. 8a). But if, on the other hand, the wave is slower and shorter (and it is made slower and shorter by the conditions which produce fibrillation) the excited state will have passed off at the

FIGURE 7. Ring preparations of atrium (left) and ventricle (right) of the dog in which Mines (1914) succeeded to produce and demonstrate true circulating excitation.

FIGURE 8. Diagrams drawn by Mines to illustrate the conditions under which circulating excitation can take place. The absolute refractory phase is indicated in black, while the condition of depressed excitability which persists after the absolute refractory period has passed (relative refractory phase) is represented by dots. See text for further explanation.

region where the excitation started before the wave of excitation reaches this point on the circle at the completion of its revolution. Not only so, but there will have been time for the excitability of the muscle to return to about the value it had at the time of the first excitation. Under these circumstances, the wave of excitation may spread a second time over the same tract of tissue (see Fig. 8b): once started in this way it will continue unless interfered with by some external stimulus arriving during that part of the cycle when the portion of the muscle stimulated is neither in the excited state nor in the condition of depressed excitability which outlasts it".

Unfortunately, here this brilliant series of highly original investigations was suddenly terminated. On a Saturday afternoon, November 7, 1914, MINES died as the result of an experiment he performed upon himself alone in the Medical College (see Fig. 9). One might wonder indeed if MINES had not died so prematurely, whether the history of the investigations into the mechanisms of tachyarrhythmias would have been totally different.

It is with great regret that we announce the death of Professor G. R. Mines, who was recently appointed to the chair of physiology at McGill University. Last winter was spent in Toronto by Professor Mines as temporary assistant to Professor Brodie, and it was only a few months ago that he commenced work in Montreal. His tragic death occurred on a Saturday afternoon, November 7th. He was engaged on a research on respiration and the heart, and his death was the result of an experiment he was performing upon himself, alone in the medical college. Professor Mines, who was born at Bath twenty-nine years ago, was educated at Bath College and the Grammar School, King's Lynn; he gained an entrance scholarship to Sidney Sussex College, Cambridge, in 1904; in 1909 he was elected to a Fellowship of his College, and became Praelector in 1911, in which year he took a first-class in the Natural Science Tripos (Parts I and II). He was additional demonstrator of physiology in the University of Cambridge from 1911 to 1914, and director of physiology in the Balfour laboratory from 1910 to 1913. Endowed with a passion for music, Mines at first thought of entering upon a musical career. His liking for natural science, however, was stimulated by Dr. P. M. Chapman, of Hereford, and it was in the development and interpretation of exact methods of recording heart action that Mines made his mark. To pursue his studies upon the hearts of lower animals, he spent months at the marine zoological stations at Plymouth, Rostock, and Naples. At the Marey Institute he mastered the technique of the cinematograph, of which he recognized the value as a record of animal movements. Possessed of great personal charm, Professor Mines had already established himself in the hearts of his associates at Montreal, and the deepest sympathy is felt for his young widow and her two little children.

Figure 9. Photograph and obituary of G.R. MINES.

GARREY (1914) completely confirmed MINES findings in ring preparations cut from turtle ventricles. Both authors also agree in their concept that fibrillation is due to multiple waves travelling in closed circuits in the syncytium. In this respect GARREY did the interesting observation that rings, two centimeters wide, cut from the base of the fibrillating ventricles of large loggerhead turtles did not recover from the fibrillary contractions; however, converting this broad

ring into a smaller and longer one it was found that "incoordinated fibrillary contractions had resolved themselves into a number of contraction waves which followed each other successively and repeatedly around and around the ring".

So one can conclude that in 1914 the efforts of the biologist MAYER and the physiologists MINES and GARREY resulted in the concept of circulating excitation and the suggestion that this phenomenon played an important role in various cardiac arrhythmias. For a detailed review of these early studies see GARREY, 1924 and RYTAND, 1966.

Circus movement in the atrium

In the next decades clinicians were to test the validity of the circus movement hypothesis as an explanation for tachycardia and fibrillation in man. This was started with great energy by Sir Thomas LEWIS and co-workers in the Medical College Hospital in London. This laboratory originally adopted the theory that tachycardia and fibrillation were based on heterogenic rapid impulse formation. In 1918, although he knew the work of Mayer, Mines and Garrey, LEWIS still "leaned to the view that irritable foci in the muscle underlay tachycardia and fibrillation". However, since he was deeply convinced of the necessity to use exact methods to support a given proposition, LEWIS determined to test this hypothesis. He originally thought that MINES' view of circus movement could easily be disproved when applied to clinical arrhythmias. However, the result was quite opposite! LEWIS and his co-workers needed a series of no less than nine papers to analyze the problem (Observations upon flutter and fibrillation, Parts I - IX 1918-1921). The last part (IX) of this series he concluded with: "We began, fortunately as it transpired, by attempting to follow the path taken by the excitation waves in flutter; it was not until we had seen pure and long-continued flutter, that the full significance of experiments on ring preparations was recognized. We were driven slowly to the conclusion that pure flutter consists essentially of a simple circus movement; in coming to that conclusion we were guided by the dramatic experiments which MINES and others had conducted upon rings of muscle. From the time when we felt able to conclude that pure flutter is comparable to this ring experiment, and that in flutter a wave circulates around a natural

opening in the muscle of the auricle, the course of the investigations became simplified".

This conclusion was based mainly on the study of only two dogs with pure atrial flutter induced either by weak faradic stimulation of the auricle, or by rhythmic stimulation rising in rate until a critical frequency was reached. Fig. 10 and 11 show the most complete results LEWIS together with FEIL and STROUD (part II, 1918-20) were able to acquire (dog KQ). During a period of pure flutter, lasting 35 minutes after rhythmic stimulation of the mid-caval region at a rate of 573 per minute, the auricles were examined by taking records from a standard lead (lead II) and from direct leads at various points on the auricular surface. The spread of the excitation wave during flutter was traced by measuring the intervals between the intrinsic deflections of the direct leads and the corresponding auricular summit in lead II. In Fig. 10 the moments of activation of the different recording sites are given in relation to the auricular complex from lead II.

FIGURE 10. The curve represents portions of two auricular complexes from lead II, taken from a dog whose auricles were fluttering. The arrows represent the times at which the excitation wave appeared, relative to this auricular complex, over various portions of the auricular surface. R.APP. = right and L.APP. = left appendix. BAND = interauricular band. L.I.V.C. = lower and U.I.V.C. = upper point on inferior vena cava. A-V = auriculo-ventricular groove. S.V.C. = superior vena cava. For actual points used see fig. 11. Ordinates = 1/10 millivolt. Abscissae = 0.01 of a second (from: Lewis, Feil and Stroud, 1920)

FIGURE 11. A natural sized outline of the dog's auricle showing the readings obtained during a period of flutter. They have been reduced to a new zero. The broken lines and arrows indicate the course taken by the excitation wave. S marks the point originally stimulated to induce flutter (Lewis, Feil and Stroud, 1920).

Figure 11 shows the spread of the excitation process, as emerged from relating the moments of activation with the exact sites of recording. In this map the intrinsic deflection in the inferior caval lead has been chosen as a new zero time. Most of the pathway taken by the activation wave during the period of flutter could be identified by this method. During one cycle of the tachycardia (beat to beat interval 0.160 sec) the wave travels from the inferior cava up along the crista terminalis and to the right auricular appendage. It then turns around the orifice of the superior cava, and passes along the interatrial band to the left atrium; a little later a new wave appears behind the inferior cava and the same sequence of activation is repeated. However, as LEWIS himself emphasized: "It remains to ascertain if this new wave is a continuation of the old one; if so, then a circus movement is proved". Unfortunately, direct measurements along the left side of the entrances of the caval veins were not obtained. Instead, indirect evidence was used to support this hypothetical part of the pathway. First of all the matter was tested by measuring the length of the supposed path of this circulating wave, and by calculating the times at which it would arrive at the several recording sites, assuming that during one cycle of the tachycardia (lasting 0.160 sec) the impulse just completed one revolution in the circuit (the length of the circuit was measured to be 137 mm). Doing this, the actual and calculated times turned out to be in close agreement. The wave arrived at each measuring point at the moment it was expected to arrive, supposing the impulse circulated as indicated in the map of Fig. 11.

A second argument was drawn from experiments in which the auricles were artificially paced from the inferior vena cava (see Fig. 12). Comparison of figures 11 and 12 makes clear that the sequence of excitation during pacing differed considerably from that during flutter. It is true that in both cases the wave spreads up the crista terminalis, but the main difference is that in case of artificial pacing the impulse spreads simultaneously to the left auricle reaching the interatrial band by a shorter path and in shorter time. On the basis of these data and arguments LEWIS decided that: "There remains little doubt that we are dealing with a wave moving around the cavae, the movement being continuous and completes once during each auricular cycle.....in some instances the wave follows the same path in the reverse direction; in other it would appear to circulate, not around the cavae, but in some other ring of muscle such as that surrounding the mitral orifice; the events vary to this extent".

FIGURE 12. An accurate and natural size drawing of the auricle of a dog, to illustrate the path taken by the excitation waves propagated artificially (at a) from the inferior vena cava. Five points on the auricle were examined and the corresponding readings are given. The readings represent the intervals between the stimulus and the corresponding excitation wave. The dotted line and arrows represent the path pursued. S.V.C. = superior vena cava and I.V.C. = inferior vena cava. P.V. = left and right pulmonary veins (Lewis, Feil and Stroud, 1950).

Later studies have come to the same conclusion (ROSENBLUETH and GARCIA RAMOS (1947); KIMURA et al. (1954); LANARI et al. (1956); HAYDEN et al. (1967)). The studies of KIMURA et al. (1954) supplied complementary data with respect to the spread of excitation at the left side of the venae cavae, where LEWIS, FEIL and STROUD were unable to take records. Fig. 13 shows the chain of electrodes they used to explore the area between the venae cavae and the pulmonary

veins, together with the resulting more complete map of the pathway of the excitation wave during flutter. The results completely confirm the conclusions of LEWIS et al.

FIGURE 13. Left: diagram of the electrodes used by Kimura et al. (1954) to make direct recordings from the left auricular surface.

Right: outline of the cephalic surface of a dog's auricle, showing the readings for the arrival of the excitation wave, which have been obtained during a flutter induced by stimulating the left appendage. Auricular cycle is 0.120 sec. Below the map a chart is given, showing the time relation of the different recording sites during one cycle of the flutter.

The involvement of obstacles in atrial flutter has been emphasized by ROSENBLUETH and GARCIA RAMOS (1947), and later by KIMURA et al. (1954). These authors found that crushing the conducting bridge between the two venae cavae, which converted the two orifices into a single obstacle, markedly facilitated the induction of flutter by rapid stimulation. Enlargement of the obstacle decreased the rate of the flutter. However, when the lesion was extended to the auriculo-ventricular groove (that is, as soon as the obstacle was not longer entirely surrounded by conducting tissue), the flutter was suddenly terminated and could no longer be reinitiated (figures 14 and 15).

FIGURE 14. Diagram illustrating the method of Rosenblueth and Garcia Ramos (1947) to facilitate the induction of atrial flutter. V.C.S., Superior vena cava; V.C.I., inferior vena cava. When the intervenous region, 1, was crushed, flutter could be readily elicited. An additional injury, 2, did not modify the rate of this flutter as long as the additional obstacle was not connected with that represented by the two cavae. But when the two obstacles were joined by the crush represented by 3, the rate of the flutter was significantly decreased. In a typical case, an increase of the effective perimeter of the obstacle from 9.0 to 12.7 centimeters, resulted in a slowing of the rate of the flutter from 7.1 to 6.3 per second.

Experiment No.	Before widening of the blocked area			After widening of the blocked area		
	cycle length sec.	frequency per min.	length of pathway (estimated) cm.	length of pathway (estimated) cm.	calculated frequency per min.	observed frequency per min.
1	0.130	461	12.0	14.9	370	414
2	0.120	500	12.0	13.0	461	480
3	0.125	480	14.0	15.5	401	428
4	0.130	461	13.0	15.0	393	414
5	0.115	522	12.0	14.0	447	454
6	0.122	492	14.0	16.0	430	423
7	0.110	545	12.0	15.0	467	545

Figure 15. Table given by Kimura et al. (1954) showing the relation between the length of the perimeter of the obstacle and the frequency of the induced flutter. The observed decrease of frequency of flutter was not so large as expected from the calculated effect of the enlargement of the circular pathway.

Over the years little attention has been paid to circus movement without the involvement of an anatomically preformed pathway. Nevertheless this has obvious consequences for the properties of a circus movement tachycardia. LEWIS was one of the few who realized that the behaviour of circulating waves in the intact heart probably would be much more complicated than in the artificial narrow rings of muscle. In his famous monograph "The mechanism and graphic registration of the heart beat" (1925) he spends a whole chapter on this subject (chapter XXVII). There he gives some theoretical considerations about the properties of circulating excitation in a simple narrow ring compared with circus movement in a sheet of muscle. Because these early ideas seem to be ignored by many following investigators and because LEWIS' theory of circus movement comes so close to the "leading circle" model as introduced in this thesis (see chapter 5), I think it

is useful to quote the relevant passage in full. First the properties of circus movement in a narrow ring are described:

"Broadly speaking, such circulating waves are governed by three factors, which in themselves are often closely interdependent.

- a. the length of the muscle path;
- b. the rate at which the wave travels;
- c. the duration of the refractory state at a given point.

If a wave is propagated along one limb of a muscular ring and returns to the point stimulated, it can find this original point responsive and traverse it in one circumstance only. The refractory period at the point in question must last a shorter time than it takes for the wave to travel the full circle. The time taken for the wave to travel will depend upon the length of path and upon the rate of propagation. Thus, if the ring measures 100 millimetres in circumference and the wave travels at 500 millimetres per second, it will complete the circuit in 0.2 of a second. If the refractory period lasts 0.15 of a second, it will end 0.05 of a second before the wave returns. If the ring measures only 50 millimetres, or the rate of propagation is 1,000 millimetres a second, it will complete the circuit in 0.10 of a second; it will return to its point of origin and, finding the muscle still refractory, will be unable to proceed. The conditions favourable to circus movement establishing itself are, therefore, a large ring, a slow rate of conduction, and a short refractory period. These three factors are largely interdependent. The rate at which the ring beats as a whole is governed by the circulation time. If the circulation time is 0.2 of a second, then 300 circuits or beats of the ring will be completed in a minute. The smaller the ring and the quicker the conduction in it, the more rapid is the beating. Upon the rate of beating will depend the length of the refractory period, it will be shorter as the beats are faster; upon the length and end-condition of the refractory period will in large measure depend the rate of conduction. Further consideration of these interrelations is much simplified if we fix our attention on the gap which exists between the crest of the advancing wave and its wake of retreat. If the circuit is completed in 0.2 of a second and the refractory period lasts 0.15 of a second, the gap is equivalent in time to 0.05 of a second or to a segment forming $\frac{1}{4}$ of the whole ring. The factors influencing this gap are easily to realize. When the path is shorter or conduction is quicker, a greater proportion of the ring will be

rendered refractory in a given period of time. When the refractory period is long, the crest of the wave has a longer time to travel before its tail begins to retreat. Each of these changes reduces the extent of the gap therefore".

<i>Decreasing and tending to abolish the gap</i>	<i>Increasing the gap</i>
Shorter path	Longer path
Quicker conduction	Slower conduction
Longer refractory period	Shorter refractory period

Then he applies these properties to the situation in which the wave is not circulating in a narrow ring but in a large sheet of muscle:

"We have been dealing, in speaking of circus movement, with a simple and narrow ring of muscle of fixed circumference; such does not exist in the auricle. It is true that there are natural rings of tissue around the mouths of the great vessels and around the auriculo-ventricular orifices, but each of these is more correctly viewed as a circular hole in a flat sheet of muscle. Thus, there is a ring adjoining the orifice; there are also outer rings, greater in circumference, at distances more removed from the orifice. These outer rings provide optional paths for the wave and introduce a new possibility, namely, change in the length of circuit travelled. Suppose that the responsive gap in a ring of tissue immediately surrounding a natural auricular orifice is represented by Fig. 310A (see Fig. 16 of this chapter), and supposing that for some reason the refractory period becomes longer, the gap will close (Fig. 310B).

Fig. 310. A. A wave (a, b, c) is circulating in a small ring of tissue: the gap is represented by the segment ac . B. If the refractory period is lengthened this gap will close and if a longer channel is open to the wave, it will take this new path (b, d, c), and a new gap represented by dc will be formed. C. Represents a wave circulating in a sheet of muscle around an orifice. In the rings immediately surrounding the orifice a gap cannot be maintained, in outer rings it will be present, and it will widen as the rings are traced peripherally (as shown by the wedge x, y, z). The rate of beating will be controlled by conditions prevailing in the ring which has the shortest gap (near x).

This closure will not end the circus movement, providing there are longer paths open to the wave; it can still circulate and will circulate, upon such a new path if the conditions are there suitable (Fig. 310B). When a wave circulates around an orifice in a sheet of muscle the size of the gap will be greater as we pass from inner to outer circles of muscle, as is shown in Fig. 310C. At any given instant the gap is represented by a wedge of tissue, its point (x) lying towards the center and its base (y z) lying peripherally. The conditions existing in the circle of muscle in which the gap is shortest, the circle which includes the point of this wedge in the diagram, are those which determine the rate of beating of the muscle sheet as a whole. That is to say, the rate of beating is not controlled by the length of path, providing sufficient optional paths are available, for the length of path is determined by the remaining factors. It is probable, too, that the rate of conduction in these circumstances would not influence the rate of beating, since a change in conduction would at once be balanced by an appropriate change in the length of path followed. It is impossible to visualize the precise paths followed by, and available to, a circulating wave in the auricle, but it would seem from the considerations here set forth that when a circus movement is established and *when shorter or longer paths can become available, the length of the refractory period is in sole control of the rate of beating*".

In a footnote to this paragraph, LEWIS gave as his view that a central aperture, although theoretically not really essential, yet will play an important role in practice, since: "it is difficult to see how a *simple* circus movement could be started in such a sheet, or how it could continue regularly without interruption or change". However, later studies have demonstrated that, according to theory, also in practice circus movement is possible without the involvement of an anatomic obstacle (WEST and COX (1960); WEST and LANDA (1962); ALLESSIE, BONKE and SCHOPMAN (1973, 1976, 1977)). WEST and LANDA have demonstrated that a tissue mass of only 32 mg of atrial muscle is already enough to produce tachyarrhythmias. This is in good agreement with our own observations which demonstrated sustained circulating excitation in a circuit with a radius of only 5 to 6 mm.

In these studies we also compared the properties of the two types of circus movement as recognized by LEWIS. In figure 8 of chapter 5 of this thesis (page 112), the two models are placed together and their respective properties are sum-

marized. If one compares the "leading circle" model, which resulted from our direct measurements, with the ideas of LEWIS, which were based mainly on interpretation of indirect data, one gets impressed by the high degree of predictive value of this piece of "arm-chair" physiology.

So, from animal experiments, it became evident that in flutter-like conditions, two distinct types of atrial activation may be in operation: one in which excitation of the two atria takes place in sequence, the direction of advance of the excitation front being strictly opposite in the right and left atrial leads, and another in which the atrial activation corresponds to a radial spread of the impulse from a circumscribed area. Similar observations have been made in patients with atrial flutter (PUECH, 1974). To explain the latter type of activity there remain two different hypotheses: that of abnormal rapid impulse formation and that of micro-reentry. With the current tools available in cardiology, there is little hope for *direct* discrimination between these two different mechanisms in man. A small localized reentry process will very much mimic a focus of rapid impulse formation since in both cases excitation waves will spread out radially, in rapid succession, to the rest of the myocardium. Our only hope therefore lies in an *indirect* identification of either mechanism. To achieve that goal it is necessary to know more about the behaviour of both mechanisms under various circumstances. Especially the study of changes in rate of an abnormal ectopic pacemaker and a micro-reentrant circuit in response to programmed electrical stimulation and the administration of drugs which specifically alter certain electrophysiologic properties of the heart seems promising (ALLESSIE et al., 1977 a, b). The relevance of the use of drugs to determine the mechanism of tachycardia in the human heart deserves to be tested. Then it might once be possible to design a number of tests which enable us to distinguish abnormal enhanced impulse formation from micro-reentry in patients.

Circus movement in the ventricles

In contrast to the much greater clinical significance of ventricular arrhythmias compared with disturbances of supraventricular origin, relatively few studies have been successful in providing direct evidence that arrhythmias of the ventricles are due to circulating excitation. This is undoubtedly caused by the greater complexity of anatomy and electrophysiology of the ventricles. These and other factors raise serious technical difficulties and impose great limitations on endeavours to analyze processes underlying ventricular arrhythmias. Like in atrial muscle, also in ventricular myocardium circus movement of the impulse is possible. The founders of the concept of circulating excitation (MAYER, MINES and GARREY) all demonstrated circulating contractions in rings cut from the walls of the ventricles. However, the suggestion that ventricular tachycardia and fibrillation in the intact heart is also based on circus movement, is derived mainly from extrapolation of direct observations on tachycardia and fibrillation of the atria. The analogy between the various arrhythmias in both chambers indeed is remarkable. On this ground most scientists have agreed that the basic mechanisms of arrhythmias in atria and ventricles are similar in nature. But, as LEWIS wrote: "Though there may be little reason any longer to doubt that circus movement occurs in the ventricle, evidence on lines similar to that obtained for the auricle is desired to complete the proof". Beneath I will review some of the studies which have contributed to obtain such proof.

The first studies which provided direct evidence of unidirectional block and circus movement in ventricular muscle were carried out by SCHMITT and ERLANGER in 1929. These investigators used strips of ventricular muscle of the turtle, put in a tissue bath divided in several compartments. In certain segments of the muscle strip conduction was depressed by pressure and local application of excess KCl. In these preparations they frequently observed partial or complete block in one direction and one to one conduction in the other direction. Also multiple responses from a single stimulus were recorded (see Fig. 17, top panel). In this experiment the strip was passed through five chambers and four partitioning rubber curtains. Segment 1 was stimulated as indicated by the arrows. The application of four stimuli with a relative long coupling interval resulted in the conduction of just four impulses through the strip. But, ... "a stimulus thrown into

segment 1 so as to produce an extra contraction immediately after the fourth contraction, called forth a long series of regular contractions arising spontaneously in segment 1 and passing thence through the length of the strip". In the lower panel of Fig. 17 the diagram which SCHMITT and ERLANGER gave to explain this phenomenon is reproduced. The strip of ventricular muscle is represented to consist of two strata of fibers (A and B), passing through a rubber membrane M. Under the membrane the fibers have been subjected both to pressure injury and to KCl poisoning (segment xy). By chance, stratum A has been more seriously affected than stratum B. As a result, in A the impulse can conduct only through segment xy in the direction $y \rightarrow x$, but not in the direction $x \rightarrow y$. An impulse originating in 1 and travelling towards 5 thus is blocked in segment xy of section A. In section B, however, the impulse succeeds in traversing region xy, although at a very slow rate. Upon leaving the region of depression at y, the impulse not only goes forward again both in A and B, but it also turns back in A and, passing through segment yx, it causes a reentrant beat in segment 1. A whole series of such reentrant beats can occur if the impulse returning through xy from 5, not only spreads into segment 1, but again excites the area of B under M. Thus a circus would be started in a comparatively small area of the ventricle, giving rise to a period of tachycardia.

FIGURE 17. Top: Multiple responses from a single stimulus. The strip of ventricular muscle was contained in five chambers, the records being numbered accordingly. Segment 1 was stimulated as indicated by the arrows. A series of beats follows an extrasystole after the fourth contraction. Two instances of this are shown. Bottom: Diagram giving a hypothetical explanation of the arrhythmias (from: Schmitt and Erlanger, 1929).

SCHMITT and ERLANGER further speculated that the special arrangement of the ventricular conduction system in the mammalian heart may serve to favour reentry. This is illustrated in Fig. 18, which is also taken from their 1929 paper. It shows a twig of the A-V bundle (D) dividing into two terminal branches which anastomose with ventricular muscle at B and C. "Under normal conditions, the impulse from D reaches B and C at approximately the same time, throwing the ventricular musculature at these points into contraction at almost the same instant. But if one of the two terminal branches happened to be the site of a local lesion, or of some other state that depressed conduction in it, the conditions might very well develop which experimentally lead to a reentrant response. Then an impulse coming from D would be blocked at A and would die out, but by way of the other terminal branch it would reach and stimulate the ventricular musculature at C. The excitation from the ventricular fibers would then reenter the Purkinje system at B and traverse the region of injury, but at so slow rate that by the time it arrived at A, the uninjured fibers there would have recovered from refractoriness and would again be excited. This excitation would immediately spread through the conducting system and reexcite the entire ventricular musculature".

FIGURE 18. *Hypothetical micro-circuit in Purkinje network of the ventricles as proposed by Schmitt and Erlanger (1929).*

As with the atria, the discussion about reentry in the ventricles has been "focussed" on the question whether the circuit should of necessity be large or whether miniature or even micro-reentrant circuits were possible. The possibility of an intraventricular echo based on antegrade conduction along one bundle branch and consecutive retrograde activation of the other bundle followed by reentry of the bundle of His and the atria, was demonstrated by MOE, MENDEZ,

and HAN (1965). The involvement of such a large reentrant loop in which the bundle branches form an important link, in some ventricular tachycardias was suggested by WELLENS et al. (1972). Subsequent observations by this author, however, revealed that this possible mechanism of ventricular tachycardia is relatively rare in man (WELLENS et al., 1974, 1975).

Other studies have shown that under certain circumstances conditions may be favourable for the assessment of small reentrant pathways. The minimal dimensions of a circuit for sustained circus movement are determined by (1) the conduction velocity of the impulse and (2) the refractory period of the fibers within the circuit. Conditions which depress conduction velocity or/and abbreviate refractory period enable the initiation of circus movement tachycardia within a small area of ventricular myocardium or within small loops of the specialized conduction system. Although action potentials and refractory periods of ventricular fibers normally are of relatively long duration, MENDEZ et al. (1969) and SASYNIUK and MENDEZ (1971) demonstrated that the occurrence of localized block at the Purkinje-muscle junctions was associated with marked abbreviation of action potential duration in the terminal Purkinje fibers just proximal to the site of block (see Fig. 19).

FIGURE 19. Conduction block at the Purkinje-muscle junction. Upper trace: electrogram taken from base of papillary muscle. Middle and lower traces: intracellular recordings from a terminal Purkinje fiber and a closely adjacent muscle fiber respectively (distance between two microelectrodes less than 500 μ). S₁ indicates the last of a series basic stimuli applied to the false tendon. S₂ and S₃: premature stimuli applied through the same pair of stimulatory electrodes. In panel A, the S₂-S₃ interval was the shortest interval with which S₃ still evoked a muscular response. In panel B, activity initiated in the false tendon by S₃ applied 1 msec earlier failed to propagate to muscle but caused an extremely brief response in the terminal Purkinje fiber. In panel C the S₂-S₃ interval was the same as in panel B and the impulse was again blocked at the junction. However, now the impulse reached muscle at other sites and returned to activate the muscle fiber and to reexcite the nearly terminal Purkinje fiber shortly after the end of the brief spike. The fact that muscle activity in the external record follows the reentrant beat indicates that the impulse emerged in muscle at a site closer to the intracellular electrode than to the external electrode. Calibrations, 100 msec and 50 mV (from: Sasyniuk and Mendez, 1971).

They showed that these brief action potentials may be of great importance in the development of intraventricular reentry, especially for the creation of circuits of no more than a few millimeters in circumference. Fig. 20 gives some examples of multiple reentries in the region of the Purkinje-muscle junction.

FIGURE 20. Same preparation as in fig. 19. Top trace: electrogram from base of papillary muscle. Middle trace: intracellular record from false tendon. Bottom trace: intracellular record from peripheral Purkinje fiber. Panel A: an example of double reentry. The S_3 impulse not only propagated back to the central Purkinje fiber, resulting in a complete reentry, but also returned again to muscle and reexcited the terminal and central fibers a second time. Panel B: an additional stimulus (S_4) induces fractionation of the reentrant wave front, as indicated by the multiple inputs in the impaled peripheral Purkinje fiber (bottom trace). On occasion S_4 was followed by as many as six non-stimulated responses (from: Sasyniuk and Mendes, 1971).

The role of depressed conduction in the occurrence of reentrant excitation after being emphasized by SCHMITT and ERLANGER (1929), has been thoroughly reinvestigated by CRANFIELD et al. (1971), CRANFIELD and HOFFMAN (1971), and WIT et al. (1972 a,b). The former authors studied the properties of slow conduction in bundles of excised canine Purkinje fibers depressed by partial encasing the false tendon in agar containing 47 mM K^+ (Fig. 21 A). Conduction velocity within the depressed segment fell as low as 5 cm/sec. All kinds of abnormalities of impulse transmission including one-way block were observed, proving that conduction delays, long enough to permit reentry, can occur in short segments of Purkinje fibers subjected to high K^+ . They further demonstrated that the slow responses in the depressed area showed the phenomena of "summation" and "inhibition" (see Fig. 21 B, C). As a result of summation an impulse can be propagated emerging out of a branch at the point where summation occurs and thus reexcite the entire heart. So far, however, it is not known whether this mechanism is operative in many of the ventricular reentrant arrhythmias.

FIGURE 21. Panel A. Diagrammatic representation of the two types of preparations employed, an unbranched bundle (above) and branched bundle (below) of false tendon. The cross-hatched area represents the agar sandwich and contains the depressed segment. M = muscle; S_1 , S_2 = stimulating electrodes at proximal and distal ends of the preparation; P, M, and D = intracellular microelectrodes used to record from the proximal end of the preparation (P), from within the depressed segment (M), and from the distal end of the preparation (D). Note that in the branched preparation the M electrode is located in the branch at a distance from the main bundle.

Panel B. Shows the phenomenon of summation. Stimulation of the ends of a depressed segment giving rise to excitation in a branch arising from the center of the depressed segment. Upper trace: proximal end; middle trace: branch; lower trace: distal end. A and C show that excitation of either end alone fails to induce an action potential in the branch. In B excitation of both ends leads to the appearance of an action potential in the branch. Calibrations: time 400 msec, voltage 100 mv.

Panel C. Shows the phenomenon of inhibition. Excitation of a branch by stimulation of one end of a depressed segment inhibited by stimulation of the other end. Upper trace: proximal end; middle trace: branch; lower trace: distal end. In A excitation of the proximal end alone gives rise to regular excitation of the branch until the distal end is also stimulated whereupon excitation of the branch is inhibited. In B excitation of both ends gives rise to no excitation in the branch; then stimulation of the distal end is stopped whereupon excitation appears in the branch. In C the first three action potentials of the proximal end excite the branch, and then excitation of the distal end is begun while excitation of the branch is inhibited. Calibration: time 400 msec, voltage 100 mv (from: Craneffeld and Hoffman, 1971).

WIT et al. (1972 a) demonstrated single reentrant beats in isolated bundles of Purkinje fibers in which conduction was depressed by perfusion with a modified Tyrode solution containing high K^+ and epinephrine (see Fig. 22).

FIGURE 22. A shows the preparation from which the tracings shown in B and C were obtained. Conduction was depressed by perfusion with Tyrode solution containing high K^+ and epinephrine. Eight recording sites are identified by numbers and the site of the stimulating electrode is labeled S. The records shown in B were obtained from sites 3 (top), 7 (middle) and 8 (bottom). The driven impulse reaches 8, 7 and 3 and is followed by a reentrant impulse that appears at sites 3 and 7 but does not elicit an action potential at site 8. The tracings shown in C were obtained from sites 3, 7, and 1. The driven impulse passes site 8 to reach site 3 but is blocked before it reaches site 1; the secondary impulse arises between sites 1 and 3, traveling forward to site 1 and retrograde to sites 3 and 7. In B and C the time marks appear at 100 msec intervals; the horizontal calibration represents 500 msec; the vertical, 100 mv (from; Wit et al. 1972, a).

The same authors succeeded in directly demonstrating sustained circus movement in closed loops of fibers of the ventricular conducting system of canine or bovine hearts, measuring only 20 to 30 mm in length. Fig. 23 shows the preparation and the multiple microelectrode recordings from the experiments of WIT et al. (1972 b). The network of Purkinje fibers and myocardium, taken from a calf heart, was depressed by a 15-minute exposure to 15 mM K^+ followed by the addition of 5×10^{-6} M epinephrine. Three intracellular recordings are shown, recorded around the loop (sites 1, 2, and 3). The first set of action potentials were elicited by a stimulus applied at S_1 ; the second group arose from a premature stimulus applied at S_2 and the rest resulted from reexcitation via circus movement without further applied stimuli. In the diagrams at the bottom the sequence of activation is drawn schematically. Panel A shows the path of the driven impulse that arises at S_1 . In B is shown the path of the premature impulse elicited at S_2 . The premature impulse is blocked in one branch and travels from 3 to 2 to 1, making a complete circus in a counter clockwise direction. On returning at site S_2 the impulse reenters site 3 and continues in the circuitous pathway to sites 2 and 1 and

so on around the ring, for a total of seven circuits.

FIGURE 23. Top: Sustained circus movement of excitation in a closed loop of Purkinje fibers. The preparation was obtained from a calf heart. Conduction was depressed by exposure to high K^+ and epinephrine. The transmembrane potentials of three fibers around the loop are recorded simultaneously. The initial set of responses arose when the drive was applied at S_1 ; activation appears more or less simultaneously at sites 1 and 2 but later at 3. Application of a premature stimulus at S_2 caused excitation to travel from S_2 to site 3 to 2 to 1 to 3 to 2 to 1 and so on to make several full circuits in a counter-clockwise direction. At the bottom the path followed by the impulse after S_1 (left) and S_2 (right) is indicated diagrammatically. Calibrations: 100 mv and 500 msec (from: Wit et al., 1972,b).

Dangerous arrhythmias in the ventricles may occur during the very first stage of myocardial infarction. Unfortunately, our knowledge of the mechanism of these arrhythmias is still very limited. As to the possible role of reentry in the acute stage of myocardial infarction, interesting experiments have recently been performed by DOWNAR et al. (1970 a, b) and JANSE and DOWNAR (1977). Using flexibly mounted microelectrodes, they followed the changes in transmembrane potential recorded from the subepicardium of both in situ and isolated intact pig's hearts immediately after coronary occlusion. Fig. 24 gives an example. During the experiment, heart rate was kept constant by artificial pacing with an interval of 390 msec. Rapidly after coronary occlusion, the action potential shortened, and its amplitude and upstroke velocity diminished. Furthermore there is a progressively increasing delay of activation and loss of resting membrane potential.

After 9 minutes of occlusion, alternation occurs, whereas after 12 minutes of ischemia the fiber got irresponsive.

FIGURE 24. Transmembrane potential of a subepicardial ventricular cell in an in situ pig heart, after occlusion of the left anterior descendens artery. The ventricle was paced at a cycle length of 390 msec. Action potential duration was progressively shortened and amplitude and upstroke velocity gradually reduced until after 12 minutes the fiber has become irresponsive (from: Downar et al., 1977b).

Ventricular arrhythmias, especially ventricular fibrillation, were seen most frequently during (1) the period of 5 to 10 minutes after onset of ischemia and (2) the period immediately following reperfusion. During both these periods, markedly depressed conduction was present together with great inhomogeneity in refractory periods in closely adjacent areas. This is illustrated in Fig. 25. The figure shows two simultaneously recorded action potentials during the development of ischemia. Stimuli were applied close to the cell of the lower trace in each panel. During control, the local refractory period was 234 msec. During ischemia refractory period progressively shortened to 140 msec. The lower panel strongly suggests that in the small area surrounding the stimulating electrode the fibers had markedly different refractory periods. A test stimulus given after 140 msec did not excite the lower cell; however, other elements in the vicinity of the stimulating electrode must have recovered their excitability as can be concluded from the fact that the upper cell was activated by the premature stimulus. The lower cell was excited only after a very long interval and the ensuing ventricular fibrillation may have been due to reentry initiated by the local inhomogeneity in spread of activation of the premature beat. Although it is, of course, impossible to demonstrate a circuitous pathway of the impulse with only two microelectrodes, this experiment of JANSE and DOWNAR (1977) clearly demonstrates that during the very early stage of myocardial infarction all circum-

stances are in favour of reentry. Slow conduction, short refractory periods, inhomogeneity in refractory periods in closely adjacent areas and the occurrence of unidirectional block, it is all that can be desired for the production of reentrant ventricular tachycardia and fibrillation.

FIGURE 25. Two simultaneously recorded action potentials from cells 1 cm apart. Stimuli were applied close to lower cell. Note shortening in refractory periods following coronary artery occlusion. Note difference in latency of test stimuli delivered 185 and 150 msec after basic stimulus (2nd and 3rd panel). In lowest panel the test pulse does not result in a regenerative response in lower cell but must have excited a more remote cell from which activity proceeded towards upper cell. The inhomogeneity in activation may have been responsible for the ensuing ventricular activation (from: Janse and Downar, 1977).

CIRCUS MOVEMENT WITH THE INVOLVEMENT OF AN ACCESSORY ATRIO-VENTRICULAR PATHWAY

There is another group of reentrant arrhythmias which deserves separate description; that is circus movement in which an anomalous accessory pathway between atria and ventricles is involved. This type of circuitous impulse propagation was already predicted in 1913 by MINES, after the existence of such anomalous connections between atrium and ventricles was demonstrated (KENT, 1892). After this first report of KENT, many cases have been described in which, either by anatomical studies or by electrophysiological evidence, anomalous pathways between atrium and ventricles have been demonstrated. Recently ANDERSON et al. (1975) have proposed a new nomenclature for the anatomical substrates underlying the varieties of the ventricular pre-excitation syndrome. In figure 26 the classification of the different anomalous connections is given. Irrespective of the type of accessory connection or bypass tract, the principle of reentry in these cases is the same: the impulse is circulating in an anatomical defined circuitous pathway. The possible pathways based upon the different types of accessory connections found in the pre-excitation syndrome have recently been discussed by DURRER et al. (1970). Depending on the localization of the accessory pathway relative to the normal A-V nodal- His pathway, the dimensions of the circuit can be either large or small. The cycle length of these tachycardias is determined by the total conduction time along this circuit. Slow conduction in the circuit and/or a long circuitous pathway will result in tachycardia with a relatively low frequency, whereas rapid conduction in a small circuit will cause tachycardia with a high rate. The development of programmed electrical stimulation of the human heart (WELLENS and DURRER, 1975) and endocardial and epicardial mapping procedures (DURRER and ROOS, 1967; GALLAGHER et al., 1976) have opened new roads towards identification of the pathway involved in an individual patient.

The chance of initiation of paroxysms of tachycardia is especially determined by the electrophysiological properties of the atrio-ventricular node and the anomalous connection. If there exists large differences in refractory periods between the two atrio-ventricular connections, conduction block of a premature beat in one of the two connections may easily occur. On the other hand if the refractory periods of both pathways are more or less equal, the reentry zone

TABLE I Definition of terms, indicating the morphological constitution of possible pathways

Definition	Subgroups	Types	Morphological origin and insertion	Composition of pathway
1. Accessory connections	A. Accessory atrio-ventricular muscle bundles	I Septal	Atrial myocardium to ventricular myocardium	Myocardium
		II Parietal (specialized)	Atrial myocardium to ventricular myocardium	Specialized tissue
		III Parietal (nonspecialized)	Atrial myocardium to ventricular myocardium	Myocardium
	B. Accessory nodo-ventricular muscle bundles	I Overlay (transitional)	Transitional cells to ventricular myocardium	Specialized tissue
		II Deep (compact node)	Compact nodal cells to ventricular myocardium	Specialized tissue
	A. Atriofascicular fibers		Atrial myocardium to penetrating bundle	Myocardium
2. Bypass tracts	B. Intranodal pathways		Alternate pathways through junctional area	Specialized tissue
3. Fasciculo-ventricular connections			Ventricular specialized tissue to ventricular myocardium	Specialized tissue

Diagram illustrating the hypothetical possibilities of preexcitation upon which the proposed nomenclature is based. The delay-producing area is localized within the transitional cell zone and compact nodal areas of the junctional specialized tissues. Preexcitation can therefore be produced (a) by an accessory muscle bundle originating and inserting in plain myocardium (1); (b) by a nodoventricular muscle bundle originating from specialized tissue and inserting in ventricular myocardium (2); (c) by an atriofascicular bypass tract inserting into the penetrating bundle distal to the zone of delay (3); (d) by hypothetical intranodal bypass tracts? (5). The possibility labelled (4) indicates the presence of fasciculoventricular fibers. Depending on their site of takeoff, size and conduction velocity these fibers could either themselves produce some amount of preexcitation by 'short-circuiting' the ventricular conduction pathways or could modify the electrophysiological behavior of a bypass situated more proximally. Another possibility exists that could produce preexcitation, that of anatomical deformations of the junctional area. This possibility is also hypothetical at the present time.

Diagram illustrating the various possible varieties of accessory connections. An accessory connection is defined as a connection INSERTING into plain ventricular myocardium. Two varieties are possible: (1) atrioventricular accessory connections and (2) nodoventricular accessory connections. The variety (1) can be further divided into parietal and septal types. The parietal type can be composed of either specialized (1a) or non-specialized (1) musculature. The second variety (2) is divided into connections between transitional cells (TC) and ventricular myocardium and the compact node (AVN) and ventricular myocardium. The other abbreviations are as follows: RA - right atrium; LA - left atrium; RV - right ventricle; LV - left ventricle.

FIGURE 26. Table and diagrams presenting a new nomenclature for the morphological constitution of the various possible accessory atrio-ventricular pathways (from: Anderson et al., 1975).

in which premature beats may initiate tachycardia can be very small. This may explain why many patients with pre-excitation seldom develop tachyarrhythmias based on a circus movement, while others seriously suffer from frequent attacks of tachycardia. It also offers a rational basis for pharmacological therapy. Drugs which tend to bring the properties of the two pathways, especially the refractory periods, closer together, can be expected to decrease the frequency of attacks. However, one should realize that drugs may not have the same effect on conduction and refractory period of accessory pathway and A-V node- His pathway when A-V and V-A conduction are compared.

Another approach is to bring the words of MINES into practice: "The best test for a circulating excitation is to cut through the ring at one point.... the vigorous circulating wave and its instantaneous arrest by section of the ring is a sight not easily forgotten". During surgery one can try to localize the anomalous connection by mapping the epicardial activation times along the A-V sulcus and then try to interrupt the accessory pathway by making a local incision along the atrio-ventricular groove, or, if the accessory pathway cannot be identified, one can try to cut the bundle of His. However, as pointed out by DURRER and WELLENS (1974): "This is a major undertaking, an ultimum refugiens which taxes the skill of the surgeon, the electrophysiological capacities of the cardiological team, and their ability to rise to the challenge of unexpected situations, which do occur all too often". This situation is a typical example of the necessity of close cooperation and electrophysiologic orientation between surgeon and cardiologist.

CIRCUS MOVEMENT IN THE ATRIO-VENTRICULAR NODE

The A-V node plays a crucial role in the normal and abnormal activation of the heart. Not only that the conduction of the A-V node is slow and its morphologic and electrophysiologic properties are rather complex, but also its position with respect to the other parts of the heart is unique in that it forms the only electrical connection between the atria and the ventricles. This special arrangement of the A-V node has made it possible to acquire much information about the function and behaviour of the node, using indirect methods. Regarding the A-V junctional area as a "black box", detailed analysis of input/output relations using His bundle recording and electrical stimulation of the atria and the ventricles, has been successful in describing mechanisms operative in the human A-V node, which in some cases could be confirmed with more direct techniques in animal experiments.

One of the most important contributions to our understanding of cardiac arrhythmias, is the demonstration of functional longitudinal dissociation as a property of the normal A-V node. Evidence for such dissociation first has been accumulated by analysis of the temporal relations between atrial and ventricular activation during premature stimulation (MOE et al., 1956). Later the presence of a dual A-V nodal conduction system could be directly demonstrated in isolated but otherwise normal rabbit hearts (MENDEZ and MOE, 1966). In figure 27 the concept of intranodal longitudinal dissociation is represented schematically. The upper part of the node is thought to be functionally and spatially dissociated into two pathways, the so-called alpha and beta pathways. Both pathways are considered to have different electrophysiologic properties especially with respect to refractory period and conduction velocity. Somewhere between the atrium and

FIGURE 27. Schematic representation of intranodal dissociation. The diagram to the left illustrates the sequence of events during an atrial echo. A premature atrial response fails to penetrate the β path but propagates through the α pathway. Once the final common pathway (FCP) is engaged, an echo may return to the atrium via the now recovered β pathway. The diagram to the right illustrates the pattern of propagation during a ventricular echo. A premature response in the His bundle traverses the FCP, finds the β pathway still refractory from the previous excitation, reaches the atrium over the α pathway, and returns through the now recovered β limb (from: Mendez and Moe, 1966).

the His bundle these pathways come together to form a final common pathway (FCP) which passes into the bundle of His. This duality in the A-V transmission system has become the basis for the explanation of both atrial and ventricular echo beats and supraventricular tachycardias arising in the atrioventricular junction. The diagrams of figure 27 illustrate the supposed sequence of events underlying an atrial echo beat (left) and a ventricular echo beat (right). An atrial premature beat is blocked in the beta pathway whereas it continues to propagate along the alpha pathway. Once the final common pathway (FCP) is reached, the beta pathway, which now has regained its excitability, is invaded retrogradely. If the impulse reaches the site of antegrade conduction block at a moment that the fibers proximal to the block have restored their excitability again, the impulse may return to the atrium as an echo beat.

A ventricular premature beat, reaching the bifurcation of the final common pathway, may equally find the beta pathway still refractory from the previous excitation; as a result the atrium is activated exclusively via the alpha pathway and the way is free for a return of the impulse to the ventricles through the now recovered beta limb. Later studies have shown that, at least in some cases, the atrium forms no obligatory link in the pathway and that a circuit is possible within the A-V node itself (MIGNONE and WALLACE, 1966; JOSEPHSON and KASTOR, 1976).

FIGURE 28. Composite record including action potentials of units in B, α and N regions. Description in text. Time calibration equals 50 msec (from: Mendez and Moe, 1966).

Figures 28 and 29 provide substantial evidence for this concept. In figure 28 an atrium electrogram is shown together with action potentials of units in β , α and N regions (the N region of the node is part of the FCP). The tracings show the responses to the basic stimulus (A_1) and a premature stimulus (A_2) applied to the right atrial roof. The basic stimulus activates both α and β pathways as well as the FCP as exemplified by the N record. The premature A_2 caused only a local response in the β cell, whereas propagation along the α pathway and N cell was successful, although conduction was considerably delayed. The β cell then showed a reciprocal response about 25 msec after the premature N response; shortly thereafter the atrial echo was recorded. A third response, reduced in amplitude, appeared in the α cell following the atrial echo; this was not propagated to the N cell and thus must be considered as abortive.

FIGURE 29. Anatomic and temporal relationship. "Time-distance" plot recorded at 35 puncture sites during passage of a premature A_2 response, its echo (A^*), and an abortive re-echo. Vertical time scale: conduction time from A_1 to the impaled nodal cell, N, in msec. Horizontal scale, conduction time from A_2 to nodal cell, adjusted to the average A_2A^* interval (150 msec). To the right of A^* , conduction time of re-echo in msec. Anatomic position of points indicated in inset sketch. Circled stars indicate site where superficial cells were characteristic of β and deeper cells of N region (FCP) (from: Mendez and Moe, 1966).

Figure 29 shows the anatomic and temporal relationship of 35 different fibers from the A-V node during the occurrence of an atrial echo. The position of each fiber is indicated on the ordinate as the time interval between the atrial complex and the corresponding action potential of the fiber during basic rhythm (A_1N_1). The vertical axis, although expressed as time, thus can be taken as an arbitrary distance scale. On the abscissa the moments of activation of the same cells during the premature beat (A_2N_2) and the echo beat (A^XN^X) are plotted. All three pathways (α , β and FCP) could be clearly identified, each pathway being represented by a relatively large number of fibers. The fibers belonging to the α pathway are plotted as solid circles, the open symbols represent elements of the β pathway, while the fibers in the final common pathway are designated by asterisks. The anatomic position of the different pathways are indicated in the inset sketch. These experiments provided the necessary direct demonstration of longitudinal dissociation in the A-V junction; it formed the basis for our present understanding of atrial and ventricular echo beats and sustained A-V nodal tachycardias.

MENDEZ and MOE (1966) also observed multiple reciprocal responses. Although they did not succeed in directly tracing the pathway of the impulse during such sustained nodal tachycardia, indirect evidence strongly suggested that this rapid rhythm was also based on reentry within the A-V node (WIT et al., 1971). There is only one example in literature in which nearly the complete pathway of the impulse through the A-V node during such a steady state tachycardia could be followed (JANSE et al., 1971). These authors used a "brush electrode" consisting of 10 conventional microelectrodes, which were inserted simultaneously in the A-V node of an isolated preparation of the rabbit heart. The ten microelectrodes were glued closely together, the tips being situated within a surface of 1.5×0.7 mm. With this technique, the moments of activation of 54 nodal cells could be determined during a sustained tachycardia, which was initiated by the induction of a single properly timed atrial premature beat. Figure 30 shows the initiation of the tachycardia. In the upper part of the figure the applied stimuli, the atrium electrogram, and simultaneous recordings of transmembrane potentials of six A-V nodal cells together with a His bundle recording are shown; the middle portion gives a ladder diagram of the sequence of activation of the fibers, while the sketch at the bottom shows the position of the cells. During basic rhythm the sequence of activation of the nodal elements is from N_1 to N_6 . During the

FIGURE 30. Simultaneous recordings of the transmembrane potentials of six AV nodal cells during initiation of supraventricular tachycardia by a premature atrial beat. The diagrams show activation times in msec during a basic beat, the induced premature beat, and the steady-state tachycardia; the time-scale is not the same as in the record. Sketch at bottom shows the position of the cells. CS = coronary sinus. The action potentials of N₁ shows some mechanical artifacts. Note that the premature atrial impulse causes a local response in N₃, indicating failure of antegrade conduction in that part of the AV node. N₄ is activated by another route (dotted line in the diagram), and N₃, N₂ and N₁ are reexcited in a retrograde fashion. This pattern persists during the ensuing tachycardia (from: Janse et al., 1971).

propagation of the premature beat this order has completely changed. Antegrade conduction of the premature impulse is blocked along fibers $N_1, 2, 3$, as can be seen from the local response in cel N_3 ; apparently these fibers belong to the β pathway. Fibers N_4-6 are activated with great delay, evidently because they are reached via the α pathway. The N_4 action potential is followed by extra non-stimulated action potentials in N_2-3 which are now excited in a reverse order compared to the basic beat. During the following period of tachycardia there was 2:1 block to the fibers $N_5, 6$ and to the bundle of His. Fibers N_1-3 were activated in a retrograde direction. Figure 31 gives the time measurements of all 54 impaled fibers during this period of supraventricular tachycardia with 2:1 A-V block.

FIGURE 31. Moments of activation of 54 AV nodal cells during steady-state tachycardia. Time scale on the ordinate indicates the temporal position of the AV nodal cells during a basic beat when the atrium was driven regularly ($t = 0$ is the atrial complex). Time scale on the abscissa indicates the temporal position of the same cells during steady-state tachycardia ($t = 0$ is the atrial complex not followed by a His complex). Note the difference in activation times during tachycardia in cells which, during a basic beat, are activated between 50 and 60 msec (modified from Janse et al., 1971).

The organization of this figure is the same as the figure of MENDEZ and MOE which showed the pathway of the impulse through the A-V node during an atrial echo (compare Fig. 29). The time scale on the ordinate gives the moments of activation of the different fibers during basic rhythm and can be interpreted as distance ($t=0$ is atrium, $t=120$ is His bundle). The abscissa indicates the temporal position of the same cells during the steady state tachycardia. The atrial complex which was not followed by a His complex was chosen as zero time. The majority of the recorded fibers belonged to the retrograde and final common pathway; only two cells were impaled lying on the antegrade pathway. Nevertheless this experiment goes as far as one possibly can go. Together with the results of MENDEZ and MOE (1966) it should be considered as the most direct demonstration and most conclusive proof of circus movement within the A-V node.

The question should be discussed whether the longitudinal dissociation of the A-V node is based on certain specific anatomic peculiarities or whether this phenomenon is solely due to differences in electrophysiological properties within the A-V node. In 1966 MENDEZ and MOE stated that the histological and electrophysiologic state of knowledge of the A-V node at that time did not permit a conclusive choice. Nevertheless, they suggested the presence of two anatomic distinct pathways: "The area between the α and β pathway (about 0.3 to 0.5 mm or less) appeared to be electrically inactive, or was overlain by a barrier of connective tissue which prevented penetration of deeper and possibly active tissue. Grossly, this area appears as a whitish streak which overlies the inferior margin of the coronary sinus orifice, or the site of the coronary venous valve. Cells of the β pathway were usually found superior to this landmark and α cells were found below it, in a direct line between the sinoatrial ring bundle and the His bundle". In 1971 JANSE et al. still hesitated to make a choice: "It is quite possible that more than two pathways are involved. Moreover, one might speculate whether these pathways are completely determined by their anatomical position. It seems possible that the way in which the excitatory waves are distributed determines which cells become α pathway and which cells β pathway".

Recently, the A-V node has been subject to combined morphological and electrophysiological investigations (BILETTE et al., 1976; ANDERSON et al., 1974, 1975). These studies have revealed several possibilities for multiple anatomic pathways in the A-V nodal area. First of all, there are distinct inputs to the A-V node. The atrial septal myocardium surrounding the A-V node, is split into

muscular bands by the orifices within the septum (fossa ovalis, inferior vena cava, and coronary sinus). Thus three main bands approach the fibrous annulus. An anterior band from in front of the fossa ovalis, a middle band between the fossa ovalis and the coronary sinus, and a third main band beneath the orifice of the coronary sinus, forming a muscular bundle in the atrial margin of the tricuspid valve septal cusp. The latter bundle is in direct communication with the inferior extension of the crista terminalis (see figure 32).

FIGURE 32. Diagrammatic representation of the interatrial septum showing the major landmarks and the area occupied by the specialized tissues of the atrioventricular node. The approaches to the node are delineated by the presence of three holes within the septum, the fossa ovalis, the inferior vena cava, and the coronary sinus, respectively (from: Anderson et al., 1974).

Histologic examination of the A-V junction further revealed that these three atrial inputs make contact with three distinct groups of *transitional cells* in the A-V node (anterior, middle and posterior group, see figure 33).

FIGURE 33. Diagrammatic representation of the AV junction. C.S. = coronary sinus. TC = transitional cells. LNC = lower nodal cells. UNC = upper nodal cells (from: Anderson et al., 1974).

These transitional cells are smaller in size than atrial fibers and show a pale staining reaction; the strands of transitional cells are separated by fibrous septa, which are not seen elsewhere in the node and indeed are a major criterion in recognizing transitional cells.

Furthermore, there is the tendon of Todaro. In man, this structure extends backwards from the fibrous collar into the sinus septum, i.e., between coronary sinus and inferior vena cava. The transitional cells join with atrial myocardium above and beneath this structure. Maybe it is not pure coincidence that in this transitional cell zone, where multiple barriers at the microscopic level exist, signs of longitudinal dissociation have been recorded (BILLETTE et al., 1976; ANDERSON et al., 1974).

Also at a lower level in the atrioventricular junction local block and re-entry seem possible. TRANUM-JENSEN (1976) showed that the *midnodal zone* is composed of tightly packed cells which have a paucity of nexus connection. The cells form a "hole" in the part of the node that is enclosed in the fibrous collar, i.e., the final common pathway. BILLETTE et al. (1976) found dissociation in activation in this area.

In conclusion one may say that the complexity in architecture of the A-V junction offers ample opportunity for fragmentation of the activation wave; it may give a plausible explanation for the fact that the A-V node is a seat of pre-deliction for reentrant arrhythmias. However, further study of the properties of circus movement with and without the involvement of anatomic obstacles seems required before a definite answer can be given.

CIRCUS MOVEMENT IN THE SINO-ATRIAL NODE

After the possibility of reentry in the sinus node was first suggested by BARKER et al. in 1943, in 1960 HOFFMAN and CRANEFIELD gave a more elaborate concept of sinus node reentry: "If the normally low conduction velocity is further reduced and local blocks are present, the following sequence of events may ensue: Excitation initiated in one part of the node may cause normally propagated activity in the atrium. This atrial activity will rapidly reach and excite some other area of the sino-atrial node. Activity will then spread slowly over some pathways in the node and reexcite the atrial muscle shortly after the end of its effective refractory period. A mechanism of this sort may cause either coupled beats, a doubling of the normal rate, or complete irregularity. A conclusive demonstration of this sequence of events would require many simultaneous records of transmembrane potential at different locations and is not presently available. However, ... coupled rhythms in rabbit and cat atria have often been observed under conditions associated with depression of nodal activity..... such coupled rhythms are most frequently associated with only a minor change in the sequence of activation of the atrium, suggesting that the initial sites of excitation for both the normal and coupled beat are quite close to the sino-atrial node". In the last years a number of clinical reports appeared in which sinus node reentry was suggested to underlay atrial echo beats and supraventricular tachycardia in man (CHILDERS et al., 1973; PAULAY et al., 1973; NARULA, 1974; WU et al., 1975). In contrast few studies have been done to test this hypothesis (HAN, MALOZZI and MOE, 1968). With only a single microelectrode at hand these investigators have attempted to follow the pathway of the activation wave within the sinus node after the induction of an atrial premature beat. In Fig. 34 the results of HAN, MALOZZI and MOE are given.

The isolated right atrium of the rabbit was driven at a slightly higher rate than the spontaneous rhythm by basic stimuli (S_1), applied at the atrial roof. After each tenth basic stimulus an early premature stimulus (S_2) was administered at the same site. In the present experiment an atrial echo could be produced repeatedly when S_2 was applied about 110 msec after S_1 . In the time that reciprocal responses were stable, 18 different fibers, both in the sinus node and in the neighbouring atrial tissue were impaled. The time relations between these 18 different puncture sites could be determined during basic rhythm, the premature beat and the reciprocal response. In the figure only 5 areas are indicated,

FIGURE 34. "Mapping" of sinoatrial echoes. Locations of stimulating and recording electrodes are shown in the diagram on the upper left. Anatomical landmarks: *ct*, crista terminalis; *as*, atrial septum; *ivc*, inferior vena cava; *cs*, coronary sinus. In each record, the upper trace shows transmembrane action potentials recorded at one of areas indicated by *Aa*, *Ab*, *SNa*, *SNb*, and *SNc* in the diagram, and the lower trace is a local atrial electrogram recorded at site *A*. Temporal sequences of these responses are plotted on the bottom graph. Activation time at each of the recording sites was selected at the point of the sharp inflection (from: Han, Malozzi and Moe, 1968).

(Aa, Ab, SNa, SNb, and SNC); each of these areas include 2 to 4 puncture sites which provided almost identical temporal patterns. In the ladder diagram at the bottom the sequence of activation of the different fibers is depicted. During the paced basic rhythm the impulse propagates from the point of stimulation to fibers Aa, Ab, SNa, SNb, and SNC in that order; the retrograde sino-atrial conduction time (measured between the moment of stimulation and the response of fiber SNC) was 60 msec. During the conduction of the premature beat the order of activation of the sinus node fibers had completely changed. Now fiber SNb is activated first (about 75 msec after S_2), followed by SNa (85 msec after S_2); the area of fiber SNC is not activated at all by the premature impulse (partial sino-atrial entrance block). The impulse leaves the sinus node somewhere in the area of fiber SNa, and the atrium is reexcited. This echo beat is indicated by open circles in the ladder diagram. Then the impulse invades the sinus node again, namely at the region that not primarily responded to the premature impulse (area SNC). After having induced yet a second response in fiber SNb, the impulse is extinguished somewhere in the node. Fiber SNa was not reentered by the impulse.

Although, because of the limited number of intranodal impalements, these data cannot be regarded as definitive proof of a circuit within the sinus node, they strongly suggest that, like in the A-V node, also in the S-A node functional dissociation may occur. However, there is also a major difference: whereas in the A-V junction premature stimulation of the atrium commonly resulted in multiple reentrant responses, as a rule only a single echo beat resulted in the sino-atrial region. Actually in the sinus node itself only abortive reentry was demonstrated. From the recorded sinus node fibers in Fig. 34, fiber SNb is the only one which showed a double response after the premature stimulus. The other fibers were activated either during the first or during the second entry of the sinus node, but they could not respond to both impulses. In other words, *sustained circus movement, so well documented in the A-V nodal region, has not been demonstrated in the sinus node.*

Experimental results rather point into another direction. Fig. 35 can serve as an example (BONKE, 1968). It shows an atrial electrogram and the transmembrane potential of a sinus node fiber, recorded from the isolated right atrium of the rabbit. During spontaneous beating a single premature stimulus was introduced in the atrium (arrow). In panel A the evoked premature beat was followed by yet another, non-stimulated, atrial response. So far this registration resembles very

much the experiments of HAN, MALOZZI and MOE (1968). In fact panel A of Fig. 35 is similar to their panel D (compare Fig. 34). Accordingly, as an isolated observation this response could be equally explained on the basis of sinoatrial reciprocation.

FIGURE 35. Recordings from a spontaneously beating isolated right atrium of the rabbit. Upper traces: atrium electrogram. Lower traces: transmembrane potential of one fiber in the sinus node. The arrow indicates the moment of premature stimulation. In panel A the premature beat is followed by a single non-stimulated beat, in panel B by two extra beats and in panel C by a whole series of rapid atrial discharges. The response of the sinus node fiber in panel A is comparable with fiber SNB recorded by Han, Malouzi and (compare with panel D, figure 34). Note that in panel C the stimulus evokes seven atrial discharges whereas the fiber in the sinus node responds with only three action potentials (from : Bonke, 1968).

However, a short time later panels B and C were recorded. Now the single premature stimulus is followed by three respectively seven atrial discharges. The sinus node fiber responded with only one respectively three action potentials. This additional observation makes it very unlikely that these short periods of tachycardia are based on sustained circus movement within the sinus node. The beat to beat interval of the atrium was about 70 msec. This is much too short for the sinus node fibers to recover their excitability and therefore they cannot form part of a possible closed circuit. Instead the runs of tachycardia can be better explained by circulating excitation in a small part of the atrial myocardium

close to the sinus node. The possibility of such a small reentrant pathway in the atrium is thoroughly discussed in the following chapters of this thesis. The sinus node itself then behaves as during rapid pacing of the atria; depending on the rate of the tachycardia it shows different degrees of sino-atrial entrance block. On the other hand it cannot be excluded that sustained circus movement may be possible in a "sick" sinus node, but as long as sustained sinus echo rhythms could not be provoked experimentally, this possible mechanism of supra-ventricular tachycardia should be considered with extreme reserve.

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Chapter 3

Circus Movement in Rabbit Atrial Muscle as a Mechanism of Tachycardia

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ABSTRACT

The isolated left atrium of the rabbit, which showed no spontaneous activity, was electrically driven for 20 beats with a cycle length of 500 msec. Tachycardia could be repeatedly initiated by the application of a single adequately timed stimulus shortly after the refractory period of the last basic beat. After the termination of the tachycardia, either spontaneously or artificially by a properly timed stimulus, this procedure was repeated. The number of beats of these tachycardias varied from just one (coupled extrasystole) to many hundreds. Surface electrograms were recorded at about 300 different sites. From the moments of activation of these sites, the spread of activation during regular driving and during the premature beat and the subsequent tachycardia could be determined. In contrast to the radial spread of the activation during basic rhythm, the impulse of the premature beat was propagated in a circular pathway. This circus movement was maintained during tachycardia. These results show that even in a small area of atrial muscle containing no anatomical obstacle the impulse can be entrapped in a circus movement. This circus movement was the underlying mechanism of the arrhythmia.

KEY WORDS

unidirectional block

surface electrogram

initiation and termination of tachycardia

atrial premature beats

reentry

■ From the many investigations that have been done to explain the mechanism underlying flutter and fibrillation of the heart, two alternative hypotheses have emerged: that of ectopic impulse formation and that of circus movement.

The possibility of a circus movement of the cardiac impulse was first mentioned by McWilliam in 1887 (1). In 1908 circus movement was demonstrated by Mayer (2) in rings cut from the bells of medusae. Mines (3, 4) and Garrey (5) described experiments, conducted at about the same time but independently of each other, on the production of circulating excitation in rings cut from cardiac tissue. Since then circus movement has been proposed frequently as the basic mechanism underlying various cardiac arrhythmias (6).

In contrast to this popularity however, it has not always been easy to provide direct evidence for this hypothesis. A definite proof of a circus movement can be obtained by following the course of the activation process from point to point during at least one interval of the arrhythmia in question. Indeed this procedure has been tried by several

investigators (7-11). A main difficulty of this approach however is the limitation of the number of electrograms that can be recorded simultaneously.

In an attempt to avoid this limitation, we used a preparation in which periods of tachycardia could be initiated repeatedly by the application of a single stimulus shortly after the refractory period. Electrograms were recorded sequentially in banks of ten and time aligned using a common reference lead. The moments of activation of more than 300 sites could be measured in this way. The maps of the spread of activation during regular driving of the preparation and during tachycardia led to the conclusion that a circus movement of the excitatory process in a relatively small area of atrial muscle was the basis for the tachycardias in our experiments.

Methods

PREPARATION

Young adult New Zealand rabbits (2-3 kg) of both sexes were anesthetized with sodium pentobarbital (20 mg/kg, iv). During artificial respiration, anesthesia was maintained with ether. All rabbits received 1,500 IU of heparin. The heart was rapidly removed and kept in oxygenated perfusion solution at 37°C. The left atrium was isolated, and the preparation, including the roof of the left atrial appendage and an adjacent part of the body of the left atrium, was fixed in a tissue bath with the endocardial side up. Care was taken to completely remove the sinoatrial node, the atrioventricular node, and the interatrial septum containing the part of the left

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This work was supported by Grant 73-054 from the Nederlandse Hartstichting.

Received February 13, 1973. Accepted for publication April 27, 1973.

atrium with the entrances of the pulmonary veins. The preparation thus obtained measured about 15×20 mm and did not show spontaneous activity.

The perfusion fluid had the following millimolar composition: NaCl 130, KCl 5.6, CaCl_2 2.2, MgCl_2 0.6, NaHCO_3 24.2, NaH_2PO_4 1.2, glucose 11, and sucrose 13. The fluid was saturated with a mixture of 95% O_2 -5% CO_2 , entered the tissue bath at the bottom, and was sucked off at the surface at a rate of 100 ml/min. The pH was kept at 7.35 ± 0.05 and the temperature at $37 \pm 0.1^\circ\text{C}$.

STIMULATION

A bipolar electrode consisting of two silver wires (diameter 0.2 mm, interelectrode distance 0.5 mm) was placed on the endocardial surface and used as the stimulating electrode. The preparation was paced at a regular rate (interval 500 msec) by constant-voltage shocks (duration 1 msec, intensity twice threshold value at most) from the stimulus isolation unit of a Grass S4 stimulator. After every twentieth beat this basic rhythm was interrupted by a test stimulus (duration 1 msec, intensity less than fourfold diastolic threshold) delivered from another Grass S4 stimulator via the same stimulating electrode. The interval between the basic and the test stimulus could be adjusted with an accuracy of 0.5 msec by a delay circuit. Before the basic rhythm was restarted, the preparation was not stimulated for about 2 seconds (Fig. 1).

RECORDING

To study the activation pattern during the early premature beat and the beats of the subsequent tachycardia, it is necessary to record the electrical activity at as many sites as possible. However, it was impossible to accommodate for example 200 surface electrodes on the preparation and to store their registrations on a recorder. For that reason, we developed the following registration method. We employed an electrode holder containing ten silver terminals mounted in a straight line. Each terminal had a diameter of 0.2 mm, and the interterminal distance was 1 mm. With this electrode array, ten unipolar surface electrograms could be recorded simultaneously, using an Ag-AgCl strip placed in the bath fluid as the indifferent electrode. The recording electrode was mounted on a solid, accurate micromanipulator (Meijer and Schreurs, to be published), which enabled us to move this electrode quickly to a new position.

For the induction of tachycardia two variables appeared to be very important, namely the position of the stimulating electrode and the moment the test stimulus was given (see Results). When we had found the right combination, registration was started. After each period of tachycardia, the multiple recording electrode was moved to another site. Thus we were able to record the electrical activity of at least 300 sites on the preparation during the onset of tachycardia. Of course this method of registration is only reliable when the spread of activation is the same during the subsequent tachycardias. Therefore, we used a control electrogram from a fixed bipolar electrode to check whether the activation times (latency between the test

stimulus and the intrinsic deflection of the electrogram of the premature beat or the beats during tachycardia) and the shapes of the complexes were the same during the different episodes of tachycardia.

DATA PROCESSING

After amplification to the level of approximately 1 v, all electrograms were stored on magnetic tape (Ampex FR 1300, tape speed 15 inches/sec). For each recording the position of the micromanipulator, indicating the relative position of the exploring electrode, was read and recorded also. For time measurements the tapes were played back at a speed of 1.875 inches/sec, and the complexes were printed out on a 14-channel Elema inkwriter (type EMT 160) running at a speed of 120 mm/sec. This procedure resulted in a time resolution of better than 1 msec. The fast part of the intrinsic deflection of the complexes was taken as the moment of activation at the relevant site. At the end of the experiment the preparation was photographed with the exploring electrode at different positions. From these photographs and the known positions of the micromanipulator during recording, the actual recording sites were defined, and maps were drawn in which the activation times of each site during the last basic beat, the early premature beat, and the beats during tachycardia were noted.

Results

INDUCTION OF TACHYCARDIA

It has been known for a long time that a single induction shock applied directly after the end of the refractory period can produce flutter or fibrillation of the heart (4, 12). Also generally accepted is the view that periods of tachycardia and fibrillation, as observed clinically in man, almost without exception are preceded by the occurrence of a premature beat (13). Recently, Bonke et al. (14) have shown that, even in a small piece of apparently homogeneous atrial muscle, the induction of an early premature beat can evoke a series of rapid atrial discharges. This phenomenon is illustrated in Figure 1. If properly timed, no current of high

FIGURE 1
Induction of a period of tachycardia by the application of a test stimulus shortly after the refractory period. Top: Surface electrogram. Bottom: Schematic representation of the stimulation pattern. The intervals between the basic stimuli are 500 msec.

FIGURE 2

Effects of a premature stimulus applied at various moments in the cardiac cycle. The numbers indicate the interval (msec) between the last basic stimulus and the premature stimulus. See text for discussion.

intensity or long duration is needed, nor is it necessary to use electrodes of large size.

Further investigation on this subject revealed that it did not matter whether the current was applied by a bipolar or a unipolar electrode or, when unipolar stimulation was used, whether the punctate electrode was the cathode or the anode. Although with anodal stimulation more current had to be applied than with cathodal or bipolar stimulation, in all cases periods of tachycardia could be evoked. This finding suggests that not the applied current itself but merely the occurrence of a premature propagated activation was responsible for this phenomenon.

Figure 2 shows some representative tracings, illustrating the possible effects of a test stimulus applied at various moments of the cardiac cycle. When the test stimulus was given 67 msec or more after the basic stimulus, a single extrasystole resulted (A). Shortening the interval resulted in runs of tachycardia (B and C). When the test stimulus was applied with an interval of 57 msec or less, no conducted response was recorded at all (D). Thus, the period in the atrial cycle in which a premature beat resulted in a series of rapid atrial

FIGURE 3

Cycle length during tachycardia plotted sequentially for three different experiments. At the beginning of the tachycardia cycle length gradually increased. Thereafter, the rate became constant. The tachycardia indicated by the triangles stopped abruptly after 78 beats; the tachycardia represented by the solid circles was terminated by a stimulus which resulted in a last shortened interval (arrow). The third tachycardia (open symbols) lasted for many minutes.

discharges was quite short. In this case it amounted to 9 msec, but often an even shorter period down to 2 msec was found. Not only was the moment at which the premature beat was elicited very critical, but also the place where the extrasystole was initiated seemed to be of even greater importance. In fact, only a few places could be found where a properly timed stimulus caused tachycardia. The most favorable place was the area where the appendage passes into the body of the left atrium.

RATE AND RHYTHM OF THE TACHYCARDIA

The cycle length during tachycardia showed a typical and consistent change during the development of tachycardia. In Figure 3 the cycle lengths of three longer periods of tachycardia, as obtained from three different preparations, are plotted sequentially. In the initial phase of tachycardia a gradual increase in cycle length was always observed. When tachycardia progressed, the cycle length became more and more regular until after about 100 beats a constant rate was reached. The cycle length varied from preparation to preparation between 100 and 150 msec when the tachycardia became steady. The end of tachycardia was abrupt: either it stopped spontaneously (triangles) or it was terminated by a stimulus (solid circles).

PATHWAY OF THE EXCITATION WAVE DURING TACHYCARDIA

Figure 4 shows some results of an experiment in which the electrical activity of more than 300 sites was recorded during regular driving of the atrium and during the initiation of tachycardia. In this figure only ten electrographic tracings (A-K) are shown. The preparation was driven at a regular rate (interval 500 msec) for 20 beats. Then a premature beat was elicited by applying a test stimulus 81 msec after the last basic stimulus. This early premature beat repeatedly resulted in a series of rapid repetitive atrial discharges.

The first electrogram of each recording represents the last regularly driven beat. The excitatory process of this basic beat showed a concentric spread from the site of stimulation; the sites in the neighborhood of the stimulating electrode (A, B, J, and K) were activated before the more distant sites.

The premature impulse was propagated in a very different way. Although the conduction velocity was reduced strikingly, the sequence of activation of sites A-F remained unaltered and the configuration of the complexes showed only minor changes. On

the other hand, at site K only a slight deflection was recorded (see arrow), and antegrade conduction failed completely toward sites J, H, and G. These sites were activated after the excitation of sites E and F, and their sequence of activation was reversed completely. This finding indicates that the impulse of the premature beat was blocked in the neighborhood of site K and that the blocked area was invaded in a retrograde way.

The change of the activation pattern was reflected also by the explicit changes in the configuration of the electrograms recorded from sites G, H, J, and K. Thus, during the propagation

FIGURE 4

Initiation of tachycardia by a premature beat. Surface electrograms recorded at ten sites on the left atrium (A-K). The atrium was driven regularly with a basic interval of 500 msec. The first arrow indicates the last basic stimulus, and the second arrow indicates the premature stimulus (interval 81 msec). The sketch at the bottom shows the sites at which the electrograms were recorded; the site of stimulation is represented by the asterisk. Note that antegrade conduction of the premature impulse failed in the direction of sites G-K. This area was activated from site F in a retrograde fashion. Sites A, B, C, etc. were reexcited from site K. This pattern persisted during the ensuing tachycardia. See text for further discussion.

of the impulse of the premature beat, the radial spread present during the basic rhythm was converted into a circus movement along the route A to B to C . . . to K. As a result, the activation wave returned to the point of its origin and got the opportunity to cause a reentrant beat.

The occurrence of reentry depends on both the stimulating efficacy of the returning excitation wave and the extent to which the place where reentry might occur has restored its excitability. Since the electrogram of the first beat of the tachycardia recorded from site A followed immediately the activation of sites J and K, obviously the restoration of the excitability of site A was sufficient to permit reexcitation by the returning activation wave. During the subsequent tachycardia, the sequence of activation established during the premature beat remained unaltered. A more complete reproduction of this experiment is shown in Figure 5, in which the time measurements of all sites from which electrograms were recorded are mapped. The isochronal lines are related to the moment of the basic stimulus (A) and the test stimulus (B-D). During the basic rhythm, the activation wave propagated radially with a conduction velocity varying from 20 to 50 cm/sec. This concentric propagation was completely lost with the conduction of the premature beat (B). Great local differences in conduction were then revealed. Conduction was best maintained toward the atrial appendage, although even there the conduction velocity was less than half as fast as it was during the basic rhythm. In the direction of the body of the atrium, the impulse was conducted only for a short distance before it died out completely. From the atrial appendage, the impulse was propagated slowly, invading the blocked area in the flank. This area was now ready to propagate the impulse, and after about 100 msec the impulse reached its starting point again.

The impulse, thus entrapped in a circuitous route, circulated for many revolutions. The subsequent two revolutions are shown in Figure 5C and D. Thus, in a small piece of atrial muscle, the occurrence of an early premature activation may entrap the excitation process in a vortexlike movement, giving rise to a period of tachycardia. No anatomical obstacle is needed to create this situation.

In a later phase of the experiment presented in Figure 5, tachycardia repeatedly stopped after the first extra beat, resulting in a "coupled extrasystole." As shown in Figure 6, the occurrence of coupled

extrasystoles was also due to a circus movement of the cardiac impulse. But now the activation front was blocked just before it should have started its third round trip. The course of the activation process during tachycardia can also be more complicated, as illustrated in Figure 7. In this experiment the spread of activation during regular driving of the atrium was radial again (A). A premature beat was elicited 60 msec after the last basic stimulus. Figure 7B shows the spread of this early impulse. The conduction of the premature impulse was blocked to all sides except for a very narrow pathway leading to the appendage. From this narrow outlet the impulse expanded and turned around its point of origin. Two separate activation waves developed in this way, the wave on each side traveling halfway around the stimulation site. These two activation waves collided 75 msec after the

FIGURE 8

Schematic representation of the effects of premature stimuli applied during tachycardia. A shows the spread of activation during tachycardia. The moment the activation wave passed the stimulating electrode was taken as zero, and isochronal lines were constructed referring to this moment. In B, C, and D the various effects are indicated in relation to the place where the crest of the circus movement was found on the moment the stimulus was given (site of stimulation is indicated by a dot). A stimulus had no effect, when the crest of the circus movement was somewhere in the hatched area, as indicated in D. When a stimulus was applied on the moment the crest of the circus movement was somewhere in the white part of D, the circus movement was either stopped (B) or reset (C).

application of the test stimulus. However, before they extinguished each other, the left wave had found an entrance in the area where antegrade conduction of the premature impulse failed, and reentry occurred (C). The impulse then once more split up in two separate waves.

However, now the left wave was blocked, apparently because the impulse traveled too fast in a circuit that was too small for every part of the route to restore its excitability. If, as in the previously described experiment (Fig. 6), this wave had been the only circulating activation wave, tachycardia would have stopped at this moment and a coupled extrasystole would have resulted. However, in this case tachycardia lasted for more than 30 beats because of the presence of the second circulating wave. After one circus movement had stopped, the other went on undisturbed and maintained the tachycardia (Fig. 7C and D).

TERMINATION OF TACHYCARDIA

Experimentally induced tachycardias often stopped spontaneously soon after they started. When spontaneous recovery did not occur, the tachycardias could always be terminated by the application of a properly timed stimulus. The timing of this stimulus had to be very accurate, as is demonstrated in Figure 8. In Figure 8A the circus movement of the impulse during tachycardia is shown; the activation times refer to the moment the activation wave passed the stimulating electrode. Revolution time amounted to 100 msec. The circus movement was interrupted when a stimulus was applied between 60 and 75 msec after the activation wave passed the area of the stimulating electrode (Fig. 8B). Stimuli given earlier found the tissue under the stimulating electrode still refractory and produced no effect at all (Fig. 8D). When the stimulus was given between 75 and 100 msec after the activation wave excited the stimulation site, a slight shortening of the interval was seen in the vicinity of the stimulating electrode and tachycardia was "reset" (Fig. 8C). A more marked shortening of the last interval was recorded when a stimulus was successful in interrupting tachycardia (Fig. 3, solid circles). This observation agrees to a large extent with the results of Janse et al. (11), who studied the effects of atrial premature beats applied during supraventricular tachycardia based on a circulating mechanism within the atrioventricular node.

Discussion

The induction of a tachycardia by the application of a single adequately timed stimulus did not depend on how current was applied, since bipolar as well as cathodal and anodal unipolar stimulation resulted in the same activation pattern. This finding suggests that a premature activation per se was responsible for the onset of tachycardia. On the other hand, it is conceivable that the pressure exerted by the stimulating electrode caused an area of reduced conductivity. However, this effect is not likely, since complexes with a sharp intrinsic deflection were recorded when the stimulating electrode was used as a recording electrode during tachycardia.

To explain the mechanism of supraventricular tachycardia, two alternative hypotheses have been proposed. In 1920, Lewis et al. (7) stated that atrial flutter was caused by a circus movement of the activation wave around the orifices of the superior or inferior caval veins or both and thus involved a large part of the atria. Other investigators (10, 11) drew attention to the possibility of a reciprocating rhythm in the atrioventricular junctional area based on a functional longitudinal dissociation. In cases of supraventricular tachycardia associated with a Wolff-Parkinson-White syndrome, it was shown that a circulating excitation between auricles and ventricles could be the underlying mechanism (15).

In other cases, however, the rapid repetitive activation waves seemed to originate somewhere in a small area of atrial muscle, and therefore a rapidly firing ectopic focus (16, 17) was assumed to be the most probable explanation, since it seemed unlikely that reentry could occur in such a small area of rapidly conducting tissue. Our results, however, show that it is possible for the activation process to be entrapped in a circuitous route even in a small segment of atrial muscle which does not contain any anatomical obstacle. The activation pattern during tachycardia looks like a vortex as is shown in Figures 5-7. The fibers in the center of the vortex are not excited, whereas during basic rhythm these fibers are activated normally. Furthermore, the activation wave propagates faster in the periphery than it does near this center. How is it possible that the fibers in the center of this vortex, consisting of excitable tissue, are not excited? A possible explanation is that the membrane potential of these fibers is held above threshold by the electrotonic influences of the depolarization front which continuously turns around this area. In this

FIGURE 6

Maps of the spread of activation when the premature beat was followed by just one atrial discharge (coupled extrasystole) in the same experiment illustrated in Figure 5. The activation wave was blocked on its second round trip. See text for further discussion.

FIGURE 7

Maps of spread of activation during basic rhythm (A), the premature beat (B), and the subsequent two beats of the tachycardia (C and D). In this experiment the premature

FIGURE 5

Maps of the spread of activation, composed of the activation times of 300 sites, during basic rhythm (A), the premature beat (B), and the subsequent two beats of the tachycardia (C and D). The site of stimulation is indicated by a black dot in A and B. A schematic drawing of the preparation (see Methods) is superimposed in A, showing trabecula running from the body of the left atrium (lower left) into the auricle (upper right). The parts of the preparation that were activated at about the same moment are indicated by different colors. The activation times are given at the site where the isochronal lines cross the circumference of the map. In A these times concern the interval between the basic stimulus and the intrinsic deflection of the electrogram complex that was recorded, whereas in B, C, and D the activation times are related to the moment the test stimulus was applied. Double bars indicate conduction block. See text for further discussion.

way the center functionally is inexcitable, and the activation wave will travel around this functional obstacle. The premature activation created the prerequisite conditions for the onset of this vortex movement, namely, (1) the early premature activation was conducted only in one direction and blocked in another (unidirectional block), and (2) the impulse traveled slowly enough on its circuitous route to enable each site of the route to restore its excitability before the impulse reached it again. The unidirectional block may be caused by asynchronism in recovery of excitability in the fibers surrounding the stimulating electrode. Since during

activation split up into two separate activation waves turning around the point of origin (B). During tachycardia one wave was blocked, but the other continued to circulate (C and D). A schematic drawing of the preparation is superimposed in A, showing trabecula running from the body of the left atrium (bottom) into the auricle (top).

basic rhythm the fibers of the white area (Fig. 5) were excited simultaneously with those of other areas, this dispersion in excitability has to be explained by a slower recovery of excitability of the fibers in the white area. The impulse of the early premature beat then may be propagated only in the direction of the fibers with the quickest recovery of excitability, while in the other directions the impulse is either not conducted at all or is conducted with so much decrement (18) that it dies out. This dispersion in excitability at the moment the premature activation wave is elicited is apparently only very slight, as is indicated by the fact that the period in the cardiac cycle in which a stimulus provoked a unidirectional block was very short, often no more than 5 msec. The fact that the most likely site for a stimulus to provoke tachycardia was near the border between the body of the left atrium and the appendage, raises the question of whether differences in refractory period between atrium and appendage exist. Further investigations are necessary to resolve this problem. The marked decrease in the conduction velocity of the impulse during the premature activation compared with that during the basic rhythm might in part be caused by the fact that in some parts of the vortex the activation wave travels in a less favorable direction. Furthermore, conduction velocity is reduced as a consequence of the sudden shortening of the interval from 500 msec to about 70–100 msec. Yamagishi and Sano (19) reported a reduction in atrial conduction velocity by 45% when they shortened the driving interval from 330 to 100 msec. Viersma (20) showed that after such a sudden interval change conduction velocity gradually decreased until only after a large number of beats a steady state was reached. This last-mentioned property of atrial muscle might explain the observation that during tachycardia the cycle length, which is determined by the revolution time of the circus movement, gradually increases and becomes regular after 100–300 beats (Fig. 3).

A circus movement will stop when the crest of the activation wave is unable to excite the tissue in the pathway ahead. This event may occur when the stimulating efficacy of the activation front is diminished or when in any part of the circuit excitability is not sufficiently restored at the time when the circulating activation wave reaches the area. The speed of restoration of excitability depends partly on the length of the preceding interval (21). The change of the conduction pattern from a radial type during basic rhythm to a circus

movement during the premature beat results in local differences in cycle length between the activation of the last basic beat and the premature beat. At those sites where antegrade conduction of the premature impulse is possible, a relatively small interval is recorded, but, at those sites where antegrade conduction fails and the impulse has to travel in a roundabout way, a much greater interval is present.

Because of these differences in preceding cycle length the premature activation wave itself induces differences in the speed of restoration of excitability. The fibers activated later on will restore their excitability more slowly, and therefore on its second round trip the activation wave will encounter tissue in a progressively less-advanced state of recovery. Consequently, during its second round trip—the first cycle of the tachycardia—the impulse seems to have an increasing chance of dying out (Figs. 6C and 7C). The foregoing is in accordance with our observations that the conduction velocity during the second round trip decreases progressively and that a premature beat is more frequently followed by a coupled extrasystole than by a longer-lasting period of tachycardia. Furthermore, the circus movement could be stopped by the application of a properly timed stimulus, as indicated in Figure 8. When a stimulus is given at the moment the excitability of the tissue under the stimulating electrode is just restored, the impulse might be conducted only in the direction towards the circulating activation front and then this circus movement will be stopped. When the stimulus is given somewhat later, the impulse might be conducted to all sides, resulting in the interruption of the existing circus movement and the initiation of a new activation wave which can travel around in the same circuit, starting a new tachycardia (Fig. 8C).

Finally, we want to stress that the ability to induce tachycardia in an excised preparation like the one described in this paper does not prove that a similar mechanism actually exists in the intact heart. It might be that the functional differences that cause one-way conduction in the isolated preparation are not present, or are present to a lesser extent, in the intact normal atrium. Furthermore, it should be mentioned that, although our results strongly point to a circus movement as the mechanism of tachycardia, the possibility that Mines (4) warned against has not been ruled out completely: "The chief error to be guarded against is that of mistaking a series of automatic beats originating in one point and travelling round it in

one direction only, owing to a complete block close to the point of its origin." However, a main argument against such a rapid automatic focus, which would mimic the circus movement in our experiments, is the observation that, despite considerable changes in cycle length of the tachycardia (Fig. 3), the next activation wave always started immediately after the completion of the foregoing one. In the case of an automatic focus whose firing frequency is independent of the spread of activation, such a relation seems highly improbable.

Acknowledgment

We are most grateful to Dr. F. J. L. van Capelle and Dr. M. J. Janse from the Department of Cardiology and Clinical Physiology of the University of Amsterdam for their help and many hours of discussion during this study and the preparation of the manuscript. We are indebted to Prof. J. Th. F. Boeles and Prof. L. N. Bouman for their support and encouragement in this investigation and to Mr. A. A. Meijer and Mr. A. W. Schreurs for their unfailing technical assistance.

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Circus Movement in Rabbit Atrial Muscle as a Mechanism of Tachycardia

II. The Role of Nonuniform Recovery of Excitability in the Occurrence of Unidirectional Block, as Studied with Multiple Microelectrodes

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Chapter 4

SUMMARY Periods of tachycardia were induced in isolated segments (15 x 15 mm) of rabbit left atrium by local application of a properly timed premature stimulus. We used a special device for multiple synchronous microelectrode recordings of responses of more than 100 fibers during the initiation of tachycardia. We clearly demonstrated circus movement of the impulse through a small area of atrial muscle as the underlying mechanism. The premature impulse was conducted antegrade in only one direction, whereas in the other directions antegrade conduction failed. The local responses of the fibers in the blocked area served as a temporary obstacle for return of the premature impulse. When these fibers recovered their excitability before extinction of the premature impulse, they were reentered

in a retrograde direction, and the impulse traveled in a circular route. During the propagation of a premature beat, local block, which set the stage for circus movement, was caused by nonuniform recovery of excitability of the atrium. We related the spread of activation of a premature impulse to the naturally occurring spatial dispersion in refractory periods and found that local conduction block invariably was associated with an area of delayed restoration of excitability. Artificial induction of differences in refractory periods by regional application of carbamylcholine made it clear that a disparity in refractory periods of only 11–16 msec between adjacent areas may be sufficient to cause local conduction block of a properly timed premature impulse.

IN A PREVIOUS PAPER¹ we reported the initial results of our studies of the mechanisms for initiation of tachycardia induced in isolated segments of rabbit atrial muscle by the application of a single premature stimulus. By

extensively mapping the spread of activation with multiple extracellular electrodes, we demonstrated that the tachycardia was based on a circus movement of the impulse through a small area of atrial muscle. This circus movement was initiated when (1) the premature impulse was conducted only in one direction and was blocked in other directions, and (2) the resulting circuitous propagation of the premature impulse took so much time that excitability was restored in the area in which the impulse was initiated at the moment it was reentered by the returning activation wave.

In this paper we are reporting more detailed information

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Supported by the Nederlandse Hartstichting, Grant 73-054.

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Received July 28, 1975; accepted for publication April 19, 1976.

on circus movement tachycardia in the atrium as obtained from multiple microelectrode recordings. Furthermore, as the occurrence of unidirectional block is the first requisite for the onset of circus movement, we investigated the circumstances under which local block may occur. Several factors might be important for the occurrence of unidirectional block: (1) nonuniform arrangement of the atrial fibers, (2) differences in the membrane responsiveness of atrial fibers, and (3) spatial dispersion in recovery of excitability. Studies on electrical activity of single cardiac fibers have shown that local conduction delay or complete failure of propagation of premature impulses can occur at the junction of two areas in which the action potentials differ in duration.²⁻⁷ Such conduction disturbances are observed when excitation in one area precedes recovery of excitability in an adjacent area. Direct determinations of refractory periods have revealed that under physiological conditions fibers in the atrium and the ventricle may have considerable variability of refractory periods. To evaluate this possible explanation for unidirectional block, we measured refractory periods at numerous sites in the atrium around the point at which a properly timed premature stimulus evoked tachycardia. These measurements were correlated with the spread of excitation during the onset of tachycardia. In addition, differences in refractory periods were induced artificially and the minimum dispersion in recovery of excitability required for the occurrence of local block was established.

[Methods]

We studied isolated segments (15 × 15 mm) of the rabbit left atrium. The preparations consisted of the roof of the atrial appendage and part of the adjacent left atrium. Most of the interatrial band and that part of the left atrium containing the entrances of the pulmonary veins were dissected and discarded. A number of experiments were performed in which differences in refractory periods were induced artificially. In these experiments isolated pectinate muscles, excised from the left atrial wall were used. The bundles were about 10 mm long and less than 1 mm in diameter. The preparation, perfusion fluid, and stimulation and recording techniques were the same as those described previously.¹ Because of the absence of any spontaneous activity, the preparations were driven at a regular rate (interval 500 msec) by applying constant voltage stimuli (duration, 1 msec, intensity, 2 times threshold) between a silver wire (diameter, 0.4 mm, insulated to the tip) placed on the tissue and an Ag-AgCl strip immersed in the perfusion fluid. To induce tachycardia, a test stimulus (duration 1 msec, intensity 4 times threshold) was introduced through the same electrodes after every 20th basic stimulus. In most of the preparations it was possible to identify one or more sites at which a properly timed premature stimulus repeatedly evoked a period of tachycardia. One or more surface electrodes were used as reference leads to ascertain whether the spread of activation during the onset of different episodes of tachycardia was the same.

MULTIPLE MICROELECTRODE RECORDINGS

To study the spread of activation of the premature beat and the subsequent beats in the tachycardia, multiple

microelectrode recordings were made around the primary site of stimulation. Figure 1 shows the device we used to facilitate this procedure.¹² Microelectrodes are placed in 10 separate holders which can be adjusted concentrically. The diameter of the circle formed by the points of the microelectrodes can be varied from 0.5 to 15 mm. Furthermore, the position of the electrodes can be changed radially over an angle of 36°. By attaching this device to a micromanipulator and placing a stimulating electrode in the center of the ring, it is possible to make simultaneous recordings that are equidistant from the site of stimulation. However, it must be emphasized that the advantage of this technique, that is, the ability to make multiple simultaneous intracellular recordings, is, to some extent, tempered by a loss of quality of the individual impalements. Therefore, the value of the method for measuring absolute values of many action potential characteristics is limited. For that reason we felt it unwarranted to try to measure absolute values of resting potential, takeoff potential, amplitude and rate of rise of phase zero of the action potential. On the other hand, for the study of changes in the response of individual fibers at the onset of tachycardia *relative* to the action potentials recorded during basic rhythm, the method is quite useful.

MEASUREMENTS OF SPATIAL DISPERSION IN REFRACTORY PERIOD

To determine whether nonuniform recovery of excitability played a role in the genesis of circus movement, we measured refractory periods at multiple sites in the atrial myocardium. The stimulation pattern described above was used. At each test point, premature stimuli (4 times threshold) were applied at progressively longer intervals. The shortest interval between the basic stimulus and the test stimulus that resulted in a propagated premature beat was taken as the time required by cells at that particular site for restoration of sufficient excitability to permit a response to a stimulus that was 4 times threshold. The values obtained in this way represent a standardized measurement of part of the relative refractory period. Reproducibility of measurements was checked frequently. Control measurements at the same site after 1 hour resulted in a variation of less than 5 msec.

ARTIFICIAL INTRODUCTION OF DIFFERENCES IN REFRACTORY PERIODS

To obtain information about the difference in recovery of excitability that is required to induce unidirectional block of a premature impulse, restoration of excitability was enhanced artificially in one part of the preparation. For these experiments isolated pectinate muscles were used because of their relative homogeneity of geometry and electrophysiological properties. The muscle bundles were put in a tissue bath, consisting of two compartments, separated by a thin rubber membrane. The muscle was pulled through a small perforation in this membrane. The two compartments were perfused by separate perfusion systems. Temperature and perfusion rate were kept constant and equal in both compartments at 37°C and 50 ml/min respectively. By adding carbamylcholine to the perfusion fluid of one compartment, both the effective and the relative refractory periods were

FIGURE 1 Photograph of the device for intracellular recording in 10 cells. The microelectrodes are fixed in individual holders which are mounted on a ring. By turning the large white wheel the position of the microelectrodes can be adjusted concentrically. With the pinion shown at the right the microelectrodes can be moved radially over an angle of 36° . A stimulating electrode is positioned in the center of the microelectrodes.

shortened in the part of the muscle studied. A concentration of $0.1 \mu\text{g/ml}$ usually was sufficient to enable the induction of early premature beats which failed to propagate into the part of the preparation in the other compartment. After unidirectional block occurred the carbamylcholine concentration was decreased gradually until all premature beats were conducted again. By comparing measurements of the refractory periods at both sides of the separating membrane, just before and after the disappearance of conduction block, the minimum dispersion in refractory periods required for the occurrence of unidirectional block could be determined.

Results

MULTIPLE MICROELECTRODE RECORDINGS DURING THE INITIATION OF TACHYCARDIA

In four of 22 experiments we obtained enough intracellular recordings to describe impulse propagation during the initiation of tachycardia. The results of a representative experiment are shown in figure 2. In this experiment runs of tachycardia were elicited repeatedly during a period of more than $\frac{1}{2}$ hour by the application of a premature stimulus 65 msec after every 20th basic stimulus. Maps of the spread of activation during basic rhythm, the premature beat, and the first 2 beats of the tachycardia are shown at the top of the figure. The dramatic change from a more or less radial spread of activation during basic rhythm into a circus movement of the impulse during the premature beat and the

subsequent tachycardia is the same as described earlier.¹ However, with the intracellular recordings now available, it is possible to trace the spread of activation more accurately. This is especially true in those areas where conduction has slowed down or is blocked completely. At the bottom of figure 2, the premature impulse was propagated in the direction of pairs A and B without any sign of decrement. However, in directions C-F conduction of the premature impulse occurred with decrement, resulting in local conduction block. The proximal fiber of pair C exhibited a small local response immediately after the premature stimulus. This consisted of a depolarization of small magnitude, slow-rising velocity, and short duration.³ This response failed to excite the more distal fiber, which was not even influenced electrotonically. Somewhat later (34 and 43 msec after the premature stimulus) both fibers of pair C were activated by the wavefront coming from the area where conduction of the premature impulse was successful (A-B). Obviously, there was sufficient recovery of excitability of the proximal fiber in pair C to permit generation of an action potential. At sites E and F the fibers close to the stimulating electrode (upper trace) were activated by the premature stimulus with a delay of 13 and 20 msec respectively. However, compared with the action potentials recorded from these fibers during basic rhythm, the premature responses were of substantially smaller amplitude and rate of rise.

FIGURE 2 Top: Maps of the spread of activation during regular (basic) driving of the preparation, the induction of a premature beat, and the first two cycles of a resulting period of tachycardia. The site of stimulation is indicated by a black dot. Activation times from more than 100 fibers were measured, and the parts of the preparation activated at about the same time (within 5 msec) are indicated by different colors. During basic rhythm the moment of the basic stimulus was taken as zero, while in the other maps the activation times are related to the moment of the premature stimulus. Double bars indicate conduction block. Bottom: Pairs of transmembrane potentials (A-F) recorded around the site of stimulation are shown around the map of the premature beat. The upper trace of each pair is recorded from a fiber close to the stimulating electrode, while the lower traces represent fibers farther away from the point of stimulation. The exact position of the fibers is indicated on the map. All records start with the last action potential of the regularly driven rhythm (interval = 500 msec). Vertical dotted lines indicate the moments of the last basic stimulus and the test stimulus, respectively. The activation times in milliseconds, added to the recordings are measured from the moment of the premature stimulus.

This strong decay of the "stimulating efficacy" of phase 0 of the action potential resulted in local conduction block of the premature impulse. This also is seen in the remarkable shortening of the duration of the premature responses in these fibers.⁴ Accordingly, the more peripheral fibers of pairs E and F (lower traces) were not activated in a direct way. The action potentials generated by these fibers at 40 and 45 msec after the test stimulus were elicited by the wavefront turning counterclockwise. At this moment, however, reentry of the proximal fibers of E and F was not yet possible. The relatively large local responses exhibited by these fibers apparently prevented their reexcitation. The proximal fiber of pair E showed only a very small electrotonic hump shortly after the distal fiber was discharged. From area D, transmembrane potentials of three fibers at different distances from the stimulating electrode are shown. The most proximal fiber (top trace) was depolarized 6 msec after the premature stimulus, the action potential being of relatively high amplitude and rate of rise. However, a little more to the periphery (middle trace), the premature impulse already had lost much of its stimulating efficacy, while in the most distal fiber (bottom trace) only an electrotonic hump was recorded. This latter fiber was activated with a delay of 66 msec by the activation wave coming from the opposite side of the preparation. Because of the long delay the impulse now could reenter the proximal fibers (74 and 76 msec after the test stimulus) despite the fact that they already had been excited. These records not only show the nature of unidirectional block in atrial muscle, they also demonstrate that the area where the impulse is blocked may serve as a temporary obstacle for the impulse to circumvent. The local responses associated with conduction block apparently prevent an early lateral invasion of the blocked area by the turning impulse.

The minimal length of the circular pathway described above is determined by at least two factors: the rate of

recovery of excitability and, partly associated with it, the conduction velocity of the impulse. When the recovery of excitability proceeds rapidly or the conduction velocity of the impulse is slow, the minimal length of the circular pathway can be small. Therefore the possibility of circus movement in very small areas of atrial muscle, as demonstrated in these experiments, is enhanced by the observed slowing of the conduction velocity of the impulse during the premature beat and the succeeding tachycardia (compare the maps in Fig. 2). As can be seen in Figure 3, this slowing of propagation may result at least in part from a decrease in efficacy of the action potential as a stimulus. Both amplitude and rate of rise decrease during the tachycardia. These changes in phase 0 of the action potential partly can be explained by Weidmann's observation¹³ that the rate of rise and the overshoot of phase 0 depolarization in Purkinje fibers depend on the takeoff potential. Since during tachycardia the atrial fibers did not repolarize fully, the takeoff potential was lower, resulting in a decrease in the rate of rise and the amplitude of the action potentials (Fig. 3).

NONUNIFORM RECOVERY OF EXCITABILITY AND UNIDIRECTIONAL BLOCK OF A PREMATURE IMPULSE

Many studies of canine and rabbit hearts have shown that atrial muscle fibers may differ considerably with respect to action potential configuration and duration. Some authors have distinguished two types of atrial fibers: atrial myocardial fibers and the so-called plateau fibers.² In Figure 4 the action potentials of six different atrial fibers in one preparation are superimposed. The distance between these particular fibers was less than 5 mm. The figure shows that in our preparations there was a wide variation in configuration and duration of the action potentials; however, two distinct types of muscle fibers could not be distinguished. This variation in shape and duration of the action potential suggests the presence of a considerable spatial dispersion in the rate of

FIGURE 3 Transmembrane potential (upper trace) and its first derivative (lower trace) during the initiation and the termination of a period of tachycardia. White arrows indicate the basic stimuli and the black arrow indicates the test stimulus. During the tachycardia, the takeoff potential, upstroke velocity, and amplitude of the action potential all decrease. During this episode of tachycardia the fiber showed some values. Calibration: horizontal bar, 1 second; upper vertical bar, 100 mV; lower vertical bar, 100 V/sec.

FIGURE 4 Superimposed action potentials of six different atrial muscle fibers recorded within an area of 25 mm² during regular driving of the atrium (interval = 500 msec). There are considerable differences in duration of the action potentials, none of them showing a distinct plateau phase during repolarization.

recovery of excitability. To study whether nonuniform recovery of excitability in atrial muscle was important for the initiation of circus movement, we measured refractory periods at numerous sites in the preparation. We found that in most preparations there was considerable dispersion in the recovery of excitability, the difference between the shortest and longest refractory periods amounting to about 30 msec. In preparations in which there was more or less uniform restoration of excitability, it was difficult or even impossible to find a stimulus site at which tachycardia could be induced. On the other hand, those premature stimuli that initiated tachycardia always were given on the border between two areas with distinctly different refractory periods. Furthermore, in relating the spread of the premature impulse which initiated circus movement, to the dispersion of refractory periods of the preparation, it was apparent that the premature impulse always propagated in the direction of the sites with shorter refractory periods, while it was blocked in the direction in which refractoriness was of greater duration (Fig. 5).

Although these results strongly suggest that spatial dispersion in refractoriness played a crucial role in the occurrence of local block, definitive proof of a causal relationship needs the additional evidence that the observed degree of nonuniform recovery of excitability per se was sufficient to produce unidirectional block of a premature impulse. In other words, one should know the *minimal* difference in refractory period between adjacent areas of the atrium which is necessary to inhibit propagation of a premature impulse. In an attempt to provide such evidence, experiments were carried out on pectinate muscles isolated from the left atrium. In these bundles dispersion in refractory periods was introduced artificially by superfusion of one half of the muscle with carbamylcholine (see Methods). Under these circumstances it was possible to elicit early premature impulses in the segment of muscle superfused with carbamylcholine which were not propagated through the remainder of the muscle. An example of such artificially

evoked unidirectional block is shown in Figure 6. The refractory periods along the bundle are plotted in the schematic drawing of the preparation at the top of the figure. The induced difference in the refractory period between the two parts of the bundle was about 24 msec. The stimulating electrode was placed close to the separating membrane on the side of the bundle superfused with carbamylcholine. At both sides of the preparation surface electrograms were recorded with bipolar leads (A and B). To record propagation and the occurrence of unidirectional block multiple microelectrode recordings were made in the normal part of the bundle. A premature stimulus applied 63 msec after the basic stimulus initiated an impulse which was conducted to the left side of the preparation, as can be concluded from the premature complex recorded at lead A. In contrast, lead B at the right side of the preparation did not record any premature activity. Between sites 1 and 2 the conduction of the premature impulse was delayed. This delay in activation was associated with an initial slight increase in the takeoff potential and amplitude of the premature response at site 2. However from this site on, in the direction of lead B, amplitude, rate of rise and duration of the premature response all decreased gradually until the impulse died out somewhere between sites 4 and 5.

To determine the *minimal* dispersion in refractory periods sufficient for the occurrence of local block, the carbamylcholine concentration was lowered gradually until the unidirectional block disappeared. At each carbamylcholine concentration refractory periods were measured at both sides of the separating membrane. Also the period in the basic cycle at which unidirectional block of a premature impulse occurred was determined. Figure 7 shows the differences in refractory periods at three carbamylcholine concentrations together with the responses of the two parts of the bundle to stimuli of different prematurity. At a carbamylcholine concentration of 0.1 μ g/ml unidirectional block occurred for premature impulses elicited between 52 and 72 msec after the basic stimulus. After the carbamylcholine concentration was decreased to 0.06 μ g/ml the difference in refractory periods diminished to 11 msec. This degree of dispersion in refractory periods still resulted in unidirectional block. However, the period in the basic cycle in which premature impulses were blocked now was narrowed to an interval of 10 msec, ranging from 63 to 73 msec after the basic stimulus. At a carbamylcholine concentration of 0.05 μ g/ml, the difference in refractory periods was only 8 msec. This was no longer sufficient to cause unidirectional block.

Thus, in this case, the minimal difference in refractory periods necessary for unidirectional block of a properly timed premature impulse can be estimated as between 8 and 11 msec. To exclude preexistent preferential conduction in one direction, in some experiments the procedure was repeated, adding the carbamylcholine to the other compartment. There was no indication of the presence of important asymmetry in conduction. The results of 14 experiments are summarized in Table 1. On the average the minimal dispersion in the refractory period for the occurrence of local block was between 11 and 16 msec. Because this falls largely within the range of the naturally occurring differences in refractory periods, which in our preparations were up to 30 msec, it can be concluded that the nonuniform

BASIC BEAT

PREMATURE BEAT

TACHYCARDIA first cycle

REFRACTORY PERIOD
DURING BASIC RHYTHM

5 mm

FIGURE 5 Maps of the spread of activation during the onset of tachycardia and of the refractory period during basic rhythm. The sites of the preparation at which a premature stimulus elicited tachycardia are indicated by asterisks. The activation times given at the outer borders of the maps refer to the moment of the basic stimulus (basic beat) and the moment of the test stimulus, respectively (premature beat and first cycle of tachycardia).

recovery of excitability which occurred spontaneously in the atrium was of decisive significance in the origin of unidirectional block and therefore in the onset of circus movement tachycardia.

Discussion

SIGNIFICANCE OF DISPERSION OF REFRACTORY PERIOD IN THE GENESIS OF TACHYCARDIA AND FIBRILLATION

Differences in refractory periods have been demonstrated among various parts of the heart, e.g., at the junction between the sinoatrial and atrioventricular nodes with the atrial myocardium,⁶ at the Purkinje fiber-muscle junction,

tion,^{4, 5, 7} and in the myocardium itself. During regular driving of the heart, Han and Moe⁸ and Janse⁹ found differences of up to 30 msec between the longest and shortest refractory periods in ventricular muscle. In the right atrium of the dog Alessi et al.¹⁰ reported a variation of 40 msec, whereas Zipes et al.¹¹ recently found that the largest difference in refractory periods between seven locations in the canine right and left atria varied between 25 and 110 msec (average, 60 msec). These authors^{10, 11} also found that this inhomogeneity was increased further by vagal stimulation. Ninomiya¹⁴ argued that this was based on nonuniform distribution of vagal fibers in the atria. In the isolated left atrium of the rabbit we found differences in refractory

periods of up to 30 msec. This degree of disparity in recovery of excitability thus is rather moderate compared to the results of other investigators.

The concept that nonuniformity of refractory periods may

play a key role in the initiation of tachycardia and fibrillation was described as early as 1913,¹⁵ and since then the significance of dispersion of refractory periods in the genesis of tachyarrhythmias has been emphasized repeatedly.^{4-11, 16-19} However, in only a few studies have attempts been made to link spatial disparity in recovery of excitability directly to reentrant activity.^{4, 20, 21} Even less information is available on what differences in refractory periods between two adjacent areas are required as a minimum for the occurrence of local block. We associated the spread of a premature impulse, initiating circulating excitation, with the spatial dispersion of refractory periods. This revealed that local block of the premature impulse invariably was linked with the presence of an area of delayed restoration of excitability. Artificial introduction of differences in refractory periods in isolated pectinate muscles by local administration of carbamylcholine made it clear that a difference in refractory periods of only 11–16 msec between neighboring areas in the atrium is sufficient to create local conduction block of an early premature beat. We therefore concluded that the physiological dispersion in refractory periods described in the atrium¹⁰⁻¹¹ seems to be adequate to create areas of block during the propagation of early premature impulses.

LOCAL CONDUCTION BLOCK AS THE CENTER OF CIRCUS MOVEMENT

The finding that relatively small differences in refractory periods may cause conduction block raises the following questions: Why does reentrant activity not occur more frequently in the normal heart, and why on many occasions did we fail to find a site at which a properly timed premature stimulus could evoke a period of tachycardia, despite the presence of apparently sufficient dispersion in refractory periods? To answer these questions one must bear in mind that for the creation of local reentrant pathways another additional condition is required: The site at which conduction of the premature impulse is blocked must be activated with such delay that excitability is restored in the fibers proximal to the block. Only then can reentry occur through these fibers. The relatively long delay that occurred before retrograde activation of the blocked area in our experiments may not be explained merely by slow conduction of the premature impulse. Cranefield and Hoffman²² have found that conduction of an impulse can be inhibited in fibers which show small local responses. The small local responses

FIGURE 6 Demonstration of local block of propagation of a premature impulse. At the top is a schematic drawing of the experimental preparation. In the right compartment, containing the normal perfusion solution, the refractory period of the atrial bundle was about 76 msec. Perfusion of the left compartment with carbamylcholine (0.1 µg/ml) shortened the refractory period to 52 msec in that part of the muscle. Electrograms were recorded at both ends of the bundle surface (marked A and B). In the normal part of the muscle multiple microelectrode recordings were made on a straight line from the separating membrane to lead B. The recordings show that an early premature impulse elicited on the left side of the separating membrane gradually failed to conduct to the right segment of the bundle, resulting in complete block of propagation.

FIGURE 7 Determination of the minimal dispersion in refractory periods necessary for the occurrence of local block. At the top, refractory periods at both sides of the separating membrane are given for three carbamylcholine (C Ch) concentrations in the left part of the bundle (0.1, 0.06, and 0.05 $\mu\text{g/ml}$). The difference in refractory periods, induced in this way, was 23 msec, 11 msec, and 8 msec, respectively. Beneath the schematic drawing of the preparation, are shown the responses of both sides of the bundle to stimuli of different prematurity, applied to the carbamylcholine-containing part of the muscle.

that occurred in our studies (e.g., the upper tracings of pairs E and F of Figure 2) were followed by some degree of refractoriness. This may explain why, despite the absence of an anatomical obstacle, the premature impulse was forced around the region of local block. Only after excitability was restored in the fibers in the blocked region were they activated retrogradely (site D in Fig. 2). An area of local block thus may not only lead to unidirectional conduction of

a premature impulse, it also may serve as a temporary obstacle around which the impulse must travel.

DIMENSIONS OF THE SITE OF LOCAL BLOCK AS THE DECISIVE ELEMENTS IN THE CREATION OF REENTRANT PATHWAYS

Whether the occurrence of local block will result in reentry depends on several circumstances, including the

TABLE 1 Results of 14 Experiments in Isolated Pectinate Muscles

Experiment	Difference in refractory periods not resulting in local conduction block (msec)	Difference in refractory periods resulting in local conduction block (msec)
29-1-75	8	15
31-1-75	13	20
5-2-75	13	18
7-2-75		
Prep. 1	11	15
Prep. 2	16	23
Prep. 3	12	19
10-2-75	13	23
12-2-75	10	14
13-2-75	11	14
14-2-75		
Prep. 1	11	13
Prep. 2	10	14
20-3-75	8	11
23-5-75	14	19
3-6-75	9	11
Mean $\pm$ SD	11.4 $\pm$ 2.31*	16.4 $\pm$ 3.99*

The degree of nonuniform recovery of excitability was controlled by varying the concentration of carbamylcholine added to one part of the muscle. For each preparation the difference in refractory periods, which was not sufficient to cause local block, is shown together with the somewhat larger difference which did result in local conduction block. On the average the minimal difference in refractory periods necessary for the production of local block was between 11 and 16 msec.

* $P < 0.001$, by paired t -test.

conduction velocity of the impulse, the duration of the refractory period, and the length of the circular pathway. In the presence of a central anatomical barrier, the length of the circuit is given by the perimeter of the obstacle. However, when such a preformed circular pathway is not involved, the dimensions of the area of local block will largely define the length of the circuit. When the conduction velocity of the impulse is high or the refractory period is long, in most cases only an "island" of block will result. For the production of reentry under these circumstances a large area of block would be required to force the impulse in a relatively long, circuitous route. On the other hand, when conduction is depressed or the rate of recovery of excitability is enhanced, a small area of block may be sufficient to cause reentry. This implies that the dimensions of a site of local block will be of great importance for the question of whether or not reentry will occur. Hence, it seems that the opportunity for reentry is not determined solely by the degree of dispersion of refractory period—which under normal conditions may be sufficient—but especially by the extension of an area in which the refractory period is prolonged. We found that only when the site of delayed restoration of excitability was large enough, could reentry occur. On the other hand, when, despite the presence of great disparities in refractory period, there were only small patches of prolonged refractoriness, there was not much chance of reentry.

It therefore seems questionable that the measurement of the differences between shortest and longest refractory periods is the decisive indicator of the risk of development of tachyarrhythmias. Also, the spatial distribution of these differences has to be taken into account. In this light, the suggestion of Han and Moe,⁸ that interventions which

facilitate the induction and perpetuation of tachycardia and fibrillation (such as vagal or sympathetic stimulation, ouabain or quinidine intoxication, hypothermia and myocardial ischemia) exert their arrhythmogenic action by an increase in temporal dispersion of the recovery of excitability, has to be extended. It is quite possible that the abovementioned interventions might favor reentrant activity, not only by increasing the dispersion of refractory periods, but also by changing conduction velocity and refractory periods in such a way that the minimal length of a circuit in which the impulses can circulate is reduced. Then, also relatively small areas of local block may start to serve as a functional obstacle for the premature impulse to circumvent, which apparently would increase the chance of reentrant activity.

Acknowledgments

We are grateful to Dr. F.J.L. van Capelle and Dr. M.J. Janse from the Department of Cardiology and Clinical Physiology of the University of Amsterdam for their help and many hours of discussion during this study. We also thank Prof. Dr. J.Th.F. Boeles and Prof. Dr. L.N. Bouman for their support and encouragement in this investigation, and A.W. Schreurs and A.A. Meijer for their unfailing technical assistance.

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Chapter 3

THE "LEADING CIRCLE" CONCEPT:

A NEW MODEL OF CIRCUS MOVEMENT IN CARDIAC
TISSUE WITHOUT THE INVOLVEMENT OF AN ANATOMICAL OBSTACLE

SUMMARY

In small pieces of atrial myocardium of the rabbit, sustained periods of circus movement tachycardia were produced by the induction of a single properly timed premature beat. With multiple intracellular and extracellular electrodes the spread of activation during the tachycardia could be analyzed accurately. Because in the present experiments there was no gross anatomic obstacle for the impulse to circulate around, special attention was paid to the phenomena occurring in the centre of the circus movement. It was found that in the absence of an inexcitable central obstacle the centre of a circus movement was invaded by multiple centripetal wavelets which converged in the very centre of the circuit. On basis of these observations a new model of circulating excitation in cardiac tissue was developed. The properties of this model (referred to as *the leading circle concept*) were compared with the behaviour of circus movement around an anatomic obstacle. It turned out that both types of circus movement tachycardia responded differently to changes in basic electrophysiologic properties as conduction velocity and refractory period. So the administration of Carbamylcholine to the tissue bath caused a marked acceleration of the leading circle tachycardia, whereas circus movement in a ring of atrial tissue was hardly affected. On the other hand, depression of conduction velocity by application of moderate doses of TTX, had a more pronounced effect on circus movement in the ring preparations compared to tachycardias based on a leading circle mechanism. Finally it is suggested to use the strength-interval curve - after some modification - to describe and predict the behaviour of a leading circle tachycardia.

INTRODUCTION

In the foregoing parts of our series of papers on circus movement in rabbit atrial muscle (1, 2), we were able to show that in a small piece of atrial myocardium the induction of a properly timed premature beat can force the impulse in a circuitous route, thus setting the stage for a period of tachycardia. Evidence was gathered that the naturally existing non-uniform recovery of excitability in the atrium was of major importance for the occurrence of unidirectional block of the premature impulse, which, of course, is a prerequisite for the onset of circus movement. Furthermore, with a technique of synchronous multiple microelectrode recording detailed information was obtained about the cellular responses during the initiation of the circus movement (2). However, thus far, no conclusive model of circus movement in the absence of an anatomic obstacle could be derived. This was mainly caused by lack of information about what is happening in the centre of a circulating impulse. In most studies on circus movement and re-entry, the model as introduced by Mines in 1913 has been used (3). This model is based on observations in ring-shaped strips of cardiac tissue and implicitly supposes the presence of some kind of gross anatomic obstacle. However, in many cases of tachycardia, like in our experimental studies, circus movement without the involvement of a central obstacle seems likely. Therefore, we do not consider the model of Mines suited to describe such a type of circus movement tachycardia.

In this paper we now report the results of multiple microelectrode recordings from the centre of sustained circus movement in small segments of isolated rabbit atrium. From these complementary studies a new model of circus movement could be derived which is applicable to circulating excitation in the absence of a non-excitable central obstacle. This model, which we called the "leading circle" concept, differs in various respects from the conventional model of circus movement. Both models respond differently to changes in basic electrophysiologic conditions like the steepness of phase zero of the action potential, the conduction velocity of the impulse and the effective and relative refractory periods. Also the mechanism of interruption of the circulating excitation may differ in both types of circus movement.

METHODS

Preparation, perfusion system, stimulating and recording techniques and the method of data processing were the same as described previously (1,2). The isolated left atrium of the rabbit was regularly paced with an interval of 500 msec. Tachycardias were produced experimentally by the induction of a single properly timed premature stimulus (duration 1 msec, intensity four times diastolic threshold). The spread of activation through the preparation was measured either with 10 unipolar surface electrodes or with a multiple microelectrode technique (4). To study the course of the excitation during tachycardia with a limited number of recording leads, several precautions have to be taken. One possible approach, which we used so far, is to induce tachycardias in a reproducible way. If the subsequent periods of tachycardia are identical, the course of the excitation wave can be mapped out, combining the results obtained during separate tachycardias. However, since slight differences in the time course of the tachycardias are accumulating, in most cases the requirement of identity was fulfilled only during the first beats. In a later stage of the arrhythmia it was hazardous to relate time measurements obtained from different episodes of tachycardia. To map the excitation process, then another procedure should be followed. The complete mapping must be accomplished during the progress of one single sustained tachycardia. Furthermore, during the mapping procedure the rate and rhythm of the tachycardia must stay constant and the mechanism underlying the arrhythmia should not change. Under normal conditions, generally the induction of a premature beat resulted only in short runs of rapid repetitive activity. However, the addition of Carbamylcholine to the tissue bath (10^{-6} - 10^{-7} g/ml), which shortened the refractory period up to about 40 - 50 msec, turned out to be an appropriate method, not only to facilitate the induction, but also to favour continuation of the tachycardia. Under these conditions we could frequently produce tachycardias which sustained for more than 30 minutes; during that time rate and rhythm of the tachycardia varied only in trifling degree. This period was sufficient to map the spread of activation either with 10 extracellular or with 10 intracellular electrodes. Successive registrations were time aligned relating the measurements to one or more fixed extracellular reference leads. This procedure did not only result in an accurate measurement of the excitation pattern during sustained tachycardia, but also allowed to make intracellular recordings from the centre of the circus movement.

RESULTS

Intracellular recordings from the centre of circus movement

Figures 1 and 2 show the results of an experiment in which the excitation process during sustained tachycardia was mapped with the multiple microelectrode technique. Similar results were obtained in two other experiments. In this case it was very difficult to evoke tachyarrhythmias under normal conditions. Only one area could be found where a premature stimulus (coupling interval 70 msec) resulted in just one extra non-stimulated beat. After addition of Carbamylcholine (3×10^{-7} g/ml) the refractory period decreased to about 40 msec. Single early premature stimuli now easily induced tachycardias which had a great tendency to continue. Not only the moment of the test stimulus, but also its point of application was now much less critical. This marked effect of Carbamylcholine was generally observed. The map at the right side of figure 1 clearly shows that the tachycardia was based on circus movement of the impulse through the myocardium. This activation pattern resulted from the time measurements of action potentials of 94 different fibers.

FIGURE 1. Map of the spread of activation in a piece of isolated left atrial muscle during a period of sustained tachycardia as constructed from time measurements of the action potentials of 94 different fibers. The impulse is continuously rotating in a clockwise direction with a revolution time of 105 msec. At the left, the transmembrane potentials of five fibers are shown which lie along the circular pathway (A - E). The moments of depolarization in msec are given together with the action potentials and the isochronic lines of the map.

All these intracellular recordings were made within a period of 24 min, during which the tachycardia showed only minimal variations in cycle length (105 msec, $\pm$ 5 msec). At the left of the map the transmembrane potentials of 5 fibers (A-E), lying along the circular route, are given. The action potentials are of markedly short duration which is caused by the influence of Carbamylcholine. It should be emphasized, however, that although the effective refractory period was shortened also by the administration of Carbamylcholine, the effect on the action potential duration was stronger than the effect on the refractory period. Therefore, under the influence of Carbamylcholine the effective refractory period outlasted the duration of the action potential, i.e., some time after full repolarization the fibers were still inexcitable.

Figure 2 shows the intracellular recordings of seven fibers located on a straight line through the centre of the circus movement. The most peripheral fibers (A and D) are the same as in figure 1. The fibers in the centre are marked by digits (1-5). As can be read from the time measurements of these fibers, the central area of the circuit was activated in a centripetal direction. From fiber A the impulse excited fibers 1,2,3 and 4 in that order. When penetrating deeper into the centre of the vortex, the centripetal wavelet lost more and more of its "stimulating efficacy" until it was unable to excite the tissue ahead. Going from fiber 1 to 4, amplitude, rate of rise and duration of the responses are all gradually decreasing, finally resulting in complete extinction of the impulse somewhere between fibers 4 and 5. At the opposite side of the circuit essentially the same sequence of events takes place. There, half a revolution time later, the circulating impulse is penetrating the centre again, travelling from fiber D to the fibers 5, 4 and 3. Again the centripetal wavelet is conducted with decrement, resulting in extinction of the impulse between fibers 3 and 2. As a result of this course of events, fibers 3 and 4, which were located in the very centre of the circus movement, only showed local responses. Because this area was invaded twice during each revolution of the impulse, the frequency of these local responses was double the rate of the tachycardia.

In a previous paper (1) we speculated about the mechanism which might explain why during tachycardia the fibers in the centre of the circus movement are not activated while during regular driving of the preparation the same fibers show a normal response: "A possible explanation is that the membrane potential of these fibers is held above threshold by the electrotonic influence of the depolar-

FIGURE 2. Same experiment as in figure 1. The membrane potentials of seven fibers (marked A, D and 1 - 5) located on a straight line through the center of the circus movement are shown. Fibers A and D are the same as in figure 1. These registrations demonstrate that the central area is activated by centripetal wavelets. Note that the fibers in the central point of the circuit (fibers 3 and 4) show double responses of subnormal amplitude. Both responses are unable to propagate beyond the center, thus preventing the impulse from short-cutting the circuit. Below the map the activation pattern is given schematically. It shows the leading circuit with the converging wavelets in the center. Block is indicated by double bars.

riorization front which continuously turns around this area. In this way the centre functionally is inexcitable, and the activation wave will travel around this functional obstacle" (1). The intracellular recordings from the centre of sustained circus movement, presented here, show that this speculation is false. The membrane resting potential of fibers 3 and 4 does not show such a degree of depolarization that they can be expected to be inexcitable. On the contrary, the centre of the vortex is continuously invaded by multiple centripetal wavelets which are blocked in the very centre of the circuit. Here the impulse encounters

FIGURE 3. Analysis of the excitation during sustained tachycardia with multiple extracellular electrodes. At the top the map of the spread of activation is given together with a schematic representation. In the latter the dimensions of the leading circuit and the centripetal wavelets are given. The hatched area in the scheme indicates the area where the centripetal wavelets are blocked. In the lower part of the figure the central part of the map is enlarged and given together with groups of three unipolar electrograms (A - F) recorded from that area. The sites of recording are indicated on the map, the most peripheral registrations being marked by asterisks. In the groups of electrograms the corresponding blocks are indicated by double bars. See text for further explanation.

fibers which are still in their refractory phase since they were already activated by another centripetal wavelet just half a revolution time earlier. In this way the circulating impulse is prevented from shortcutting the circuit, whereas the area of converging wavelets serves as an "obstacle" for the impulse to turn around. In the diagram beneath the map in figure 2 the sequence of excitation is summarized schematically. It can be described as a "leading" circulating wave front, which not only activates the periphery but from which also centripetal wavelets are emerging which collide in the centre of the circuit. In this experiment the diameter of the leading circle was about 6 mm. Hence the total length of the circular pathway can be estimated to be about 20 mm.

Extracellular recordings from the centre of circus movement

Although the technique of multiple microelectrode recording allows detailed analysis of the electrical behaviour of different individual fibers in a wide range of experimental circumstances, its use is limited because of the delicacy of the technique. Since measurement of the course of excitation through cardiac muscle with extracellular leads is much more simple and because surface electrodes have a much wider field of application, we also examined whether the mechanism in the centre of circus movement could be studied with this method. Figure 3 shows the results of an experiment in which the spread of excitation during a sustained tachycardia was mapped with multiple extracellular leads. In this experiment again Carbamylcholine (2×10^{-7} g/ml) was added to the tissue bath to facilitate the induction and to favour the perpetuation of tachycardias. The map reveals that during tachycardia the impulse was rotating in a clockwise direction with a revolution time of 80 msec. At the bottom of the figure the central part of the map is enlarged and is given together with a number of electrograms recorded from this area. Accurate analysis of these electrograms again demonstrates the existence of multiple centripetal wavelets converging into the centre of the circuit. In this case, however, rather than that the wavelets collided at one single point, there was a longdrawn area where the centripetal impulses were blocked. In the diagram in the right upper corner of the figure the spread of excitation in the central area is given schematically as it can be recognized from the multiple electrograms. The area of block is indicated by hatching. In the tracings the corresponding blocks are indicated by double bars. In all panels the tracings indicated by

an asterisk is recorded at the most peripheral site. (Note that the lower trace of panel D is the same as the upper trace of panel E.) As in case of intracellular recording (see figure 2), in the area of collision the electrograms show two clearly separated responses. For instance, in panel C, the upper trace (recorded from the left site) shows an activation 75 msec after the zero reference. The lower trace (right site) shows a single response at 22 msec. Since the cycle length of the circus movement was 80 msec this means a time lapse of 27 msec between the activation of the two closely approximated sites. The middle trace of panel C shows that this delay is not caused by slow conduction, but by a conduction block between the two sites. During each cycle of the circus movement the middle trace shows two distinct complexes. The first, being of low amplitude ($t=77$ msec), is almost simultaneous with the deflection in the upper trace. The second complex ($t=25$ msec) is linked with the lower recording. Thus, each of the two complexes of the middle trace belongs to an other centripetal wavelet coming from opposite directions and colliding at the middle one of the three recorded sites. The same can be seen in panel D. In the other panels block of centripetal wavelets can also be recognized. There, however, the double complexes in the middle traces are less clearly separated because the detour of the impulse around the site of block is relatively small. Thus also with extracellular recordings one can get the necessary information to identify this type of circus movement.

The effect of Carbamylcholine, Tetrodotoxin and Temperature on circus movement tachycardia

To elucidate whether the above described type of circus movement responds differently to changes in electrophysiologic properties compared to circus movement around an anatomical obstacle, we studied the effect of Carbamylcholine, Tetrodotoxin (TTX) and temperature on the rate of both types of tachycardia. In these experiments the left atria of two rabbits were isolated and put together in the same tissue bath. One preparation was kept intact while the other was transformed into a ring-like structure by making multiple incisions as indicated in figure 4. Cutting the preparation in this way, the length of the ring was about 40 mm. With the single stimulus method sustained circus movement was then induced in either preparation. Generally in ring preparations tachycardia could be induced more easily than in the intact segments of the atrium; the tachycardias in the ring also

tended to last longer. Multiple extracellular recordings confirmed that the tachycardia was based on a circuitous sequence of excitation through the ring. Like in the intact preparation also in the ring preparations the site of application of the test stimulus was important, but in most preparations it was not too difficult to find an area where the test stimulus started tachycardia. The rate of tachycardia in the ring was always lower than the one in the intact segment of the atrium. After revolution time of both independent circulating excitations had become constant, Carbamylcholine or TTX was added to the tissue bath and the effect on cycle length of the two tachycardias was recorded.

FIGURE 4. Panel A: endocardial view of intact segment of left atrium consisting of part of the body of the atrium with the adjacent appendage. To transform the preparation into a ring-like structure, multiple cuts were made as indicated by the dotted lines. Panel B: ring preparation of atrial muscle as it results from the multiple incisions.

Figure 5 shows the effect of Carbamylcholine (2×10^{-6} g/ml). The example is representative for four experiments. The concentration of Carbamylcholine used caused a shortening of the effective refractory period up to about 40 - 50 msec; conduction velocity increased only slightly. As a control, the interval of a spontaneously beating isolated right atrium was also recorded. Prior to the administration of Carbamylcholine the interval of sinus rhythm was 365 msec.

FIGURE 5. The effect of Carbamylcholine (2×10^{-6} g/ml) on sinus rhythm, tachycardia in a ring preparation and tachycardia in an intact segment of the atrium. All three rhythms respond differently to the administration of Carbamylcholine. Whereas sinus rhythm is slowed down and the tachycardia in the intact atrium is accelerated, the circus movement in the ring of atrial muscle is hardly influenced.

The revolution time of the impulse through the ring of atrial muscle amounted to 168 msec, whereas the cycle length of the tachycardia in the intact preparation was 143 msec. All three rhythms responded differently to the action of Carbamylcholine. As expected, sinus rhythm slowed down, and the beat to beat interval of the isolated right atrium increased from 365 to 800 msec. In contrast the circus movement in the ring of atrial muscle was hardly affected. Carbamylcholine only caused a slight shortening of the cycle length from 168 to 162 msec which can adequately be explained by the minute increase in conduction velocity brought about by the drug. The tachycardia in the intact piece of atrial muscle, however, showed a marked acceleration, the circulation time being substantially reduced from 143 to 116 msec. Frequently the application of Carbamylcholine caused a sudden

termination of the tachycardia in the intact preparation; in the ring-like preparations this was never observed. This marked difference in the effects of Carbamylcholine on the two different atrial preparations strongly points to the existence of two different types of circus movement tachycardia (see Discussion).

Three experiments were done to study the effect of TTX on circus movement with and without an anatomic obstacle. Figure 6 shows an example. TTX was administered in such low doses (3×10^{-7} g/ml) that impulse conduction was slowed down but not completely blocked. Measurement of strength-interval curves before and during the administration of TTX made clear that in these doses TTX did not affect the time course of the restoration of excitability. In both models of circus movement the decrease in stimulating efficacy and conduction velocity of the impulse induced by TTX resulted in a deceleration of the tachycardia. However, the effect was more pronounced in the ring preparation than it was in the intact segment of the atrium. In this example the revolution time of the circulating excitation in the ring preparation increased from 138 to 172 msec (25%), while in the intact piece of atrial muscle revolution time increased from 117 to 129 msec (11%). This difference in behaviour again suggests a different underlying mechanism.

FIGURE 6. Effect of TTX (3×10^{-7} g/ml) on the coupling interval of circus movement tachycardia in a ring preparation and in an intact piece of atrial myocardium. Both tachycardias are decelerated. However, the effect is more pronounced in the ring preparation than in the intact atrium.

The effects of temperature on circus movement tachycardia was studied in three cases. It is known that cooling of the heart causes a decrease in the rate of depolarization, whereas the duration of the action potential is markedly prolonged (5,6). Consequently conduction velocity is depressed and the refractory period is lengthened. These changes in electrophysiologic properties resulted in a marked diminution of the rate of the tachycardia. Figure 7 gives the temperature dependency of circus movement in a ring-like structure and in an intact piece of myocardium. At 37°C revolution time was 172 and 134 msec respectively. Lowering the temperature resulted in a gradual lengthening of the beat to beat interval. At 29°C the cycle length of the tachycardia in the ring of atrial tissue had increased from 172 to 288 msec (67%) whereas the interval in the intact preparation had become 215 msec (60% increase). Thus, although in both models the effect on the circulation time was considerable, no clear difference in their response to temperature changes could be observed.

FIGURE 7. The effect of temperature on tachycardia in a ring of atrial muscle compared with the effect on circus movement in an intact atrial segment. In both cases, lowering of temperature caused a marked prolongation of the revolution time of the impulse.

DISCUSSION

The leading circle concept

From the results described above, a new model of circus movement in cardiac tissue emerges. When there is no anatomic obstacle which defines the length of a circular pathway, the circuit in which the impulse circulates, is completely defined by the electrophysiologic properties of the fibers composing the circuit. *Under these circumstances the smallest possible pathway in which the impulse can continue to circulate, is the circuit in which the stimulating efficacy of the circulating wave front is just enough to excite the tissue ahead which is still in its relative refractory phase.* In other words, in this smallest circuit possible, which we designated as the "leading circle", the head of the circulating wave front is continuously biting in its own tail of refractoriness. Because of this tight fit, the length of the circular pathway equals the "wave length" of the circulating impulse (i.e. product of conduction velocity and refractory period). In the centre of the leading circle, dimensions are too small for a sustained circus movement. Within this area a circulating impulse would encounter tissue where excitability has not yet recovered sufficiently. As a consequence, the conduction velocity of the impulse would be secondarily depressed below some minimal value where successful impulse propagation is no longer possible. In fact, the area within the leading circle is activated by centripetal wavelets that arise from the leading circle and collide in the very centre of the circus movement. Going from the leading circuit to the periphery, the length of a circular pathway is getting longer and longer. Since a longer pathway indicates a longer revolution time, it is evident that also the fibers in the periphery will be excited by wave fronts emerging from the leading circle, rather than that they form part of a longer circuit. In figure 8 the leading circle concept is compared with the model of circus movement around an obstacle as proposed by Mines (3). The main features of the leading circle model are: 1) The length of the circuit is not determined by anatomic but by electrophysiologic properties. 2) The dimensions of the circuit are not fixed but may change with alterations in electrophysiologic properties, such as conduction velocity, upstroke of the action potential, and time course of recovery of excitability. 3) Because there is a tight fit be-

tween the crest and the tail of the impulse there is no excitable gap in the circuit. This implicates that a wave front (or stimulus) of greater efficacy than the circulating impulse is required to interfere with the leading circle. This may have some important implications for the degree of protection of such a focus of reentrant activity. 4) Because the centre of the circuit consists of excitable tissue, under some circumstances the impulse may succeed to cross the centre. In comparison with the Mines model such a short-circuit offers an additional mechanism for the interruption of tachycardia. 5) Whereas the revolution time of a circus movement in a large anatomically defined circuit is inversely related to the conduction velocity of the impulse, in the leading circle model revolution time is primarily proportional to the time course of recovery of excitability of the fibers composing the circuit (see below).

CIRCUS MOVEMENT AROUND ANATOMIC OBSTACLE (MINES 1913)

1. Length of circular pathway determined by perimeter of anatomic obstacle.
2. Length of circular pathway fixed.
3. Excitable gap between crest and tail of the impulse (white part of circuit).
4. Impulse can not shortcut the circuit.
5. Revolution time inversely related to conduction velocity.

CIRCUS MOVEMENT WITHOUT ANATOMIC OBSTACLE (LEADING CIRCLE MODEL)

1. Length of circuit determined by conduction velocity, stimulating efficacy, and refractory period.
2. Length of the circuit can change with alterations in electrophysiologic properties.
3. No gap of full excitability.
4. Shortcut of the circuit possible.
5. Revolution time proportional to refractory period.

FIGURE 8. Comparison of the properties of circus movement with and without the involvement of a central anatomic obstacle.

Theoretical considerations on the leading circle model

As indicated by Lewis (7), three factors must be considered in any theory of circus movement, namely the length of the conduction pathway (P), the conduction velocity (V), and the duration of the refractory period (R). According to this theory, a circulating excitation can only take place when the path length equals or exceeds the product of conduction velocity and refractory period ($P > VR$). When in case of circus movement within an anatomically defined loop of excitable tissue the wave length of the impulse (VR) is shorter than the length of the circuit (P), there is a gap of full excitability between the crest and the tail of the circulating impulse. In this situation conduction velocity is not influenced by changes in refractory period. Since revolution time = $\frac{P}{V}$, and the length of the pathway is fixed, in this type of circus movement revolution time varies inversely with conduction velocity (rev. time $\sim \frac{1}{V}$). However, in many cases the situation cannot be described adequately in this simple manner. When the revolution time of a circulating excitation is too short to allow full recovery of excitability of the fibers in the circuit the depolarization wave will travel through relatively refractory tissue and consequently the conduction velocity will be reduced. In this situation conduction velocity (V) and refractory period (R) are no longer independent variables but on the contrary they are inextricably linked (8).

In the leading circle concept the length of the circuit is variable, being defined by and equal to the wave length of the circulating impulse ($P = VR$). This means that the revolution time of the impulse is *not* determined by the length of a given circuit but by the length of the circulating impulse itself. Since revolution time = $\frac{P}{V}$, and $P = VR$, in the leading circle model the revolution time is proportional to the refractory period (rev. time $\sim R$). In fact, however, the process of recovery of excitability is too complex to be described by just one single value of the duration of refractoriness. A more accurate way to express the time course of restoration of excitability is to measure the strength-interval curve. Such a curve depicts the minimal stimulus strength which is required to induce a propagated excitation at different moments of prematurity, or, vice versa, it gives the refractory period for stimuli of different intensities. With some modification, this well-known and easily measurable electrophysiologic relationship gives a much better description of the properties of the leading circle than the oversimplified relation: revolution time $\sim R$. In the pathway of the leading circle

the situation is very similar to the situation described by the strength-interval curve. In either case, the strength of the stimulus, respectively the stimulating efficacy of the circulating wave front, is just enough to initiate, respectively maintain propagation. Therefore on the ordinate of the strength-interval curve we can replace stimulus-strength by stimulating efficacy of the circulating impulse. On the abscissa the interval then represents the interval of the tachycardia i.e. the revolution time of the circus movement (see fig. 9). This modified strength-interval curve thus describes the main feature of the leading circle model, i.e. the existence of a tight fit between the head and the tail of the circulating impulse. In the pathway of the leading circle, under all circumstances, the relation between stimulating efficacy and revolution time of the impulse will fit the strength-interval curve. The area to the left of the curve refers to those circuits which, like the central area of the leading circle, are too small to accommodate sustained circus movement. The area to the right of the modified strength-interval curve represents the situation that exists in the circuits which have a longer pathway than the leading circle.

Changes in rate of leading circle tachycardia by alterations in electrophysiologic properties

Figure 9 shows how the strength-interval curve can be used to predict changes in revolution time of a leading circle tachycardia in response to changes in some basic electrophysiologic properties. Panel A illustrates the effect of a decrease in amplitude and rate of rise of the action potential (taken together as stimulating efficacy). When during a certain tachycardia with a revolution time a , the stimulating efficacy of the circulating wave front is diminished, according to the modified strength-interval curve, the revolution time will increase from a to b . The experimental imitation of this situation by the application of TTX indeed revealed such a decrease of the rate of the tachycardia (see fig. 6). In case of a shortening of the refractory period the strength-interval curve shifts to the left (broken line, panel B). Assuming that the stimulating efficacy of the circulating excitation keeps constant, the given shift of the strength-interval curve results in a shortening of the revolution time from a to b . The observed acceleration of the leading circle tachycardia by the application of Carbamylcholine (see fig. 5) is in good agreement with this explanation.

FIGURE 9. Explanation of observed changes in rate of the leading circle tachycardia on the basis of a modified strength-interval curve. In the modified strength-interval curve, on the ordinate, stimulus strength is replaced by stimulating efficacy of the circulating impulse. On the abscissa, the interval then stands for revolution time of the circulating excitation.

Panel A: A decrease in stimulating efficacy of the circulating impulse causes a lengthening of the revolution time of the leading circle from *a* to *b*.

Panel B: A shortening of the refractory period (shift of the strength-interval curve to the left) results in a shortening of the revolution time.

Panel C: Slowing down of the tachycardia by a combination of decrease in stimulating efficacy and lengthening of the refractory period.

Panel D: At a sudden increase in heart rate i.e. the onset of tachycardia, the stimulating efficacy of the impulse is gradually decreasing while refractory period is shortened. The net effect of these changes on the coupling interval of the tachycardia depends on the relative degree of these changes. In this case the net result was a lengthening of the revolution time from *a* to *b*.

However, a selective change either in stimulating efficacy or in refractory period is rarely met in nature. Most changes in electrophysiologic properties, occurring spontaneously or induced by certain cardiac drugs, affect both the upstroke of the action potential and the time course of restoration of excitability. In panels C and D of figure 9 two examples of such a miscellaneous influence on the leading circle model are given. In panel C the combination of a decrease in stimulating efficacy and a lengthening of the refractory period is shown. Both the shift of the strength-interval curve to the right (broken line curve in panel C) and the decrease of the stimulating efficacy of the action potential cooperate to prolong the revolution time of the leading circle from *a* to *b*. As a consequence the tachycardia will decelerate considerably. Since cooling of the heart exerts the above-mentioned combination of effects, we can take the temperature experiments for comparison (see fig 7). The relatively strong slowing of the tachycardia which we found to be associated with lowering of the temperature again seems to confirm the validity of the model. The same effect can be expected from cardiac drugs as quinidine, procainamide and β -adrenergic blocking agents (8).

In other situations the changes in stimulating efficacy and refractory period will have an opposite effect on the interval of the tachycardia. An example of a situation in which a decrease in stimulating efficacy is coupled with a shortening of the refractory period is a sudden increase in heart rate. After a sudden increase in heart rate, amplitude and dV/dt max of the action potential are gradually decreasing until only after a large number of beats (hundred or more) a new steady-state is reached (9,10). At the same time the refractory period is gradually shortened (11). The sudden onset of a paroxysm of tachycardia thus is followed by a period in which the stimulating efficacy of the impulse gradually decreases while the refractory period is shortened. Whether as a result of these changes the cycle length of the tachycardia is gradually shortening (warming-up phenomenon) or lengthening, will depend on the degree to which both parameters are influenced. The paroxysms of tachycardia as produced experimentally in the isolated left atrium of the rabbit always showed a gradual increase in cycle length during its initial phase. As tachycardia progressed, cycle length became constant after about 100 beats (1). Panel D of figure 9 shows how this phenomenon can be explained on basis of the leading circle model. The solid curve represents the strength-interval curve during basic rhythm (interval 500 msec). The dotted line represents the strength-interval curve after the tachycardia has reached a steady state (interval about

130 msec). During the first 100 beats of the tachycardia the strength-interval curve is gradually shifting to this steady state value. At the same time the stimulating efficacy of the circulating wave front is gradually falling down. When, as in this example, the effect of the decrease of the stimulating efficacy on the revolution time exceeds the effect of the shortening of the refractory period, the net result will be a gradual lengthening of the interval of the tachycardia from a to b . When on the other hand the shortening of the refractory period is more marked, and the change in the upstroke of the action potential is more moderate, the net result can be opposite. After initiation of circus movement the revolution time will then get shorter, and the tachycardia will show the "warming-up" phenomenon.

Changes in dimensions of the leading circuit

The diameter of the leading circuit in the present experiments was about 6-8 mm. This means that a minimal area of approximately 30-50 mm² of atrial muscle is required to accommodate the circus movement. This is in remarkably good agreement with previous studies of West and Landa (12) who demonstrated that it is not possible to induce a sustained arrhythmia in rabbit atrial segments smaller than a critical mass of 30 mg. An important feature of the leading circle model is that the length of the reentrant pathway is determined by the electrophysiologic properties of the tissue. Changes in refractory period, conduction velocity and stimulating efficacy will all influence the dimensions of the circuit. An acceleration of the process of recovery of excitability shortens the wave length of the circulating excitation. Since in the leading circle concept the length of the circular pathway equals the wave length of the impulse, a shortening of the refractory period will lead to a shortening of the circuit. The decrease in cycle length of tachycardias in intact pieces of atrial myocardium as observed after application of Carbamylcholine (see fig. 5) is therefore probably associated with a shortening of the circular pathway. Such a reduction of the dimensions for circus movement can also explain why Acetylcholine and its derivatives highly favour the induction and perpetuation of tachycardia (13) and why these drugs frequently convert tachycardia into fibrillation (14). Regarding fibrillation as a state in which more than one wavelet is circulating through the myocardium (15), the chance for the development of this situation is high, either in large hearts or in tissue in which small

circuits are possible.

Finally we want to emphasize that the two different types of circulating excitation, as opposed in this paper, should be considered as extremes. In such a complex organ as the heart there is a good chance of intermingling of these forms of circus movement. If, instead of the presence of a gross anatomic obstacle, there are pathways of preferential conduction, circus movement tachycardia may arise, which properties are somewhere in between the qualities of the leading circle model and circus movement in a large loop of cardiac tissue.

ACKNOWLEDGEMENTS

We gratefully acknowledge Prof. Dr. L.N. Bouman and Dr. T. Blangé for the long hours of inspiring discussion during this study and Bebbly van der Mars for secretarial help.

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