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Real-time contact force measurement for catheter ablation of cardiac arrhythmias

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Summary
Radiofrequency (RF) energy nowadays enjoys an indisputable value as the dominant energy source for the treatment of various arrhythmias amenable to catheter ablation, which has gradually replaced surgical techniques for the treatment of supraventricular and ventricular arrhythmias with electric, thermal, light, mechanical and chemical means. It has become obvious in recent years that the success and sustainable effect of the ablation may depend on a critical understanding of the biophysics of lesion creation and its control.

Biophysics of lesion formation
Current radiofrequency (RF) generators use an unmodulated sine-wave alternating current (AC) at a frequency of 300–750 kHz (too high to provoke rapid myocardial depolarisation and thus the induction of atrial or ventricular fibrillation) to deliver RF energy in a unipolar fashion between the electrode tip of the ablation catheter and a dispersive electrode/cutaneous patch, while body tissue in-between serves as a resistive medium. During RF energy delivery, the electrical energy is converted to thermal energy at the electrode-tissue interface by resistive or ohmic heating, and is transmitted by conduction to the myocardial tissue and into the blood pool. The passage of current produces resistive heating within a narrow rim at the electrode-tissue interface, while deeper tissue layers are heated as a result of passive heat conduction [1–3]. Resistive heating is proportional to the square of the current density, which, in turn, is inversely proportional to the square of the distance from the ablation electrode. As a result, resistive heating decreases with the distance between the ablation electrode and the electrode-tissue interface to the fourth power [4]. In-vivo studies further showed that lesion size is also proportional to RF power delivery due to a greater current density at the electrode tip [5]. Therefore, increasing the heating effect at the electrode-tissue interface would also increase the temperature gradient, and thus lesion size and depth, and that monitoring levels of power delivery during RF ablation would be a convenient indicator of lesion formation. However, current flow is affected by impedance changes. The higher the impedance, the greater the voltage drop and hence the higher the amount of electrical energy dissipating as heat. Since laboratory equipment forming most of the ablation circuit has a high conductance and so minimises power loss, the major dissipation of RF energy occurs from the electrode into the circulating blood pool, resulting in a smaller lesion size [6]. Although greater tissue heating has been shown to be associated with larger lesion size, temperatures ≥100 °C result in boiling of tissue water and coagulum formation (resulting from protein denaturation) at the tip of the catheter, producing a rapid increase in impedance and loss of effective tissue heating [7]. Adequate tissue heating is reflected by an impedance drop of 5–10 ohms, whereas a significant rise may occur in the case of excessive tissue heating, with charring or vaporisation of surrounding blood and steam formation within tissue, which may result in myocardial rupture and tamponade [1, 8–12]. In fact, larger initial impedance decreases significantly increase the risk of a subsequent significant impedance increase and adverse effects [2]. Another important determinant of lesion formation is duration of RF delivery. Steady-state temperatures are reached within seconds at the electrode-tissue interface, but deeper tissue layers require much more time for passive heat conduction. Various studies have reproducibly shown that the half-time of lesion growth is ca. 8 seconds and a maximum lesion volume is achieved when RF energy is applied for 30–40...
seconds [5, 13]. Finally, once myocardium is exposed to heating, loss of membrane excitability and a drop in conduction in tissue occurs as a sign of tissue injury. Whereas excitability remains almost normal at temperatures below 45 °C, reproducible irreversible injury of tissue occurs at above 50 °C. Of note, these effects have been shown to be exclusively thermally mediated and unrelated to the dissipation of high-frequency current (see below) [6, 14–16].

Advances in ablation catheter technology

Catheter technology has significantly advanced in recent years with the common goal of optimising the size and transmurality of RF lesions while minimising collateral damage.

One of the first modifications for improved efficacy and control of tissue heating and, hence, lesion size, was the incorporation of thermocouples or thermistors within or on the tip electrode of the catheter, in order to measure temperature values during RF ablation. This allows an automatic adjustment of the applied power as a function of the target temperature (commonly 55 °C or 60 °C) based on a closed-loop control system, thus potentially preventing an impedance rise and steam/soft thrombus formation [7]. Notably, the thermocouples/thermistors do not provide accurate information on tissue temperature values, but measure the temperature only at the electrode-tissue interface, thereby often recording falsely low measurements owing to heat loss to the blood pool [18]. Moreover, RF power is significantly reduced in areas of low blood flow, which causes the electrode to reach the target temperature at lower power levels as a result of poor cooling despite low tissue temperatures, such as in a deep pouch in the subeustachian cavotricuspid isthmus or dilated and poorly contracting atria and ventricles [9]. Increasing the electrode target temperature to 65 °C or 70 °C in these areas where lesion size is adversely affected because of low local blood flow, only marginally increases delivered RF power, but also increases the risk of thrombus formation and impedance rise [20–24]. A larger electrode (up to 8–10 mm in length) results in an increased electrode surface area exposed to the blood pool, allowing greater cooling, better maintenance of targeted RF power and thus larger and deeper lesions in various areas [10, 25]. The subsequent development of active electrode cooling by means of fluid irrigation (a closed loop system with circulating fluid within the electrode or an open irrigation system with saline flushed through openings in the electrode) has allowed greater independence from the limited electrode-tissue interface cooling produced by luminal blood flow [24, 26, 27].

The preceding account shows that RF power and duration, electrode size and tissue temperature are all well-known determinants for effective heating of the myocardial target site and thus for efficient lesion creation. Lesion creation is also obviously and very importantly determined by the contact between the energy delivering electrode and the target tissue, although until recently this has not been considered a quantifiable parameter. Maximising the contact area reduces the electrode surface area exposed to the low impedance shunt, i.e., the luminal circulating blood pool, thus favouring current delivery to the target tissue. Poor contact and spatial instability may lead to unnecessary heating of the blood pool, coagulum formation and failure to achieve the required myocardial temperatures regardless of the voltage and power applied. The key to effective and safe treatment with RF catheter ablation is to control lesion size, which implies controlling tissue temperature, although this cannot currently be determined in vivo. Controlling lesion size is important for ablation efficacy – particularly for substrates requiring multiple ablations, such as linear lesions making strategies such as for typical/atypical atrial flutter, atrial fibrillation and ventricular tachycardia.

The role of catheter contact: a historical perspective

The correlation of electrode-tissue contact with lesion size and thus the importance of catheter contact during RF ablation has been recognised as a major determinant of lesion formation through in-vitro experiments performed in the 1990s [13, 28]. In one study, serial RF lesions were created with RF energy delivery of 90 seconds and power adjusted to maintain a constant electrode-tissue interface temperature at 80 °C on canine free right ventricular free-wall preparations. The electrode was carefully positioned perpendicularly to the myocardial surface prior to energy delivery and the force of contact between the electrode and tissue was varied between 0 and 400 mN (0–40 g). The authors observed that lesion depth increased statistically significantly, but not dramatically, with higher contact forces (CFs) between 10 mN (~1 g) and 400 mN (~40 g) in a linear relationship, while power settings were titrated to maintain a constant electrode-tissue interface temperature. Higher CFs (i.e. >40–400 mN) did not result in significantly increased lesion depth because of downregulation of delivered power to maintain elec-
trode-tissue interface temperature. In the second study, in anaesthetised dogs with hearts exposed through a median sternotomy, a catheter holder was used to position a 4-mm ablation electrode with four different levels of contact with the epicardial surface (+3 contact or +1 contact – electrode pressed 3 mm or 1 mm into epicardium, respectively; 0 contact or –5 contact – electrode lightly touching or retracted 5 mm above, respectively). The results clearly showed that an increase in electrode-tissue contact is associated with a temperature rise and impedance drop, and an increase in lesion diameter and depth. When the electrode was positioned without contact and thus with zero force 1 mm above the endocardium, the lesion size was dramatically reduced since no direct resistive heating of the myocardium occurred. One important observation was that better contact resulted in deformation of the tissue surface, allowing the ablation electrode to embed slightly and the contact to improve, thereby resulting in more efficient formation and control of the lesion. Accordingly, poorer contact was associated with significant increases of power to maintain a constant electrode-tissue interface temperature (fig. 1) [13, 28]. Furthermore, differences in stiffness, plasticity or elasticity of the target tissue may influence the “dose-response” of contact force and thus lesion size by altering contact area. These observations clearly indicate that insufficient contact results in smaller lesions with regards to volume and depth, but it has taken many years to overcome the technical challenges of an accurate and reliable implementation of real-time contact sensing modalities in RF catheters, which is why until now operators have had to rely on passive tactile feedback, fluoroscopic appearance and movement of the catheter tip, electromyograms (EGMs), intracardiac ultrasound and/or a combination of the “traditional” measurements discussed above, such as local electrogram attenuation, electrode temperature and impedance drop, as surrogate measures [29]. However, new technologies now allow continuous and accurate real-time evaluation of tissue contact by means of precise measurement of real-time CF, yielding valuable insights for a better understanding of lesion creation and its control.

A recent study investigated the time-dependent evolution of CF, quantified as the force-time integral (FTI) in gram-seconds (gs) or as the area under the CF curve, with regards to lesion size while RF power and peak CF were maintained constant in an in-vitro model simulating the beating heart. An open-tip irrigated catheter incorporating a dynamic force sensor (Tacticath, see below) was attached to a movable mount. Radiofrequency energy was delivered during constant contact (20 g, simulating the pattern in the fibrillating heart chamber), variable contact (20 g peak and 10 g nadir) and intermittent contact (20 g peak and 0 g nadir) for 60 seconds with 17 cc/min of irrigation. The variable and intermittent contact protocols, modelling organised rhythms, were performed at 50 and 100 movements/min and a systole:diastole time ratio of 2. The authors observed that measured FTI was highest in the constant contact group, and was intermediate and lowest in the variable and intermittent contact groups, respectively. Furthermore, FTI correlated linearly with lesion volume in an equivalent proportion between the different contact groups. These results clearly showed that a clinical strategy of achieving a variable contact pattern (without exceeding safe peak CF values) might allow effective and predictable lesion creation. Likewise, an intermittent contact pattern should be recognised in order to avoid ineffective RF delivery and, eventually, conduction recovery. Furthermore, respiratory movements may also have repercussions on FTI and thus lesion size, which is why FTI over one to two respiratory cycles may be useful to anticipate lesion size and its control [30].

**Available systems**

Currently, four systems, allowing continuous and accurate real-time estimation/measurement of tissue

![Figure 1: Better contact results in deformation of the tissue surface, allowing the ablation electrode to embed slightly and the contact to improve, thereby resulting in more efficient formation and control of the lesion (fig. 1b as compared with fig. 1a).](image-url)
ongoing after recent strategic changes of the above-mentioned companies, such as the takeover of Endosense by SJM (figs 2 and 3).

The earliest available technology was the robotic catheter remote contact sensor system IntelliSense® Fine Force Technology using two force sensors that grip the shaft of any ablation catheter, which protrudes from the system-inherent steerable sheath (Artisan). The ablation catheter was pulsed four times per second <1.5 mm in and out of the Artisan sheath and coaxial force data (based on a resistance measurement of the moving catheter) was acquired with each pulse thereby also eliminating static friction as a source of force noise [31, 32].

The TactiCath™ (formerly by Endosense SA, Geneva, Switzerland) is a 3.5 mm open irrigated-tip ablation catheter, with a thermocouple and a force sensor in its distal part between the second and third electrode. This force sensor consists of an elastic polymer (i.e., deformable body, elastomer) and three circumferentially aligned optical fibres allowing the calculation of CF as a vector sum (based on deformation of the elastic polymer), thus providing information on the total force and the direction of the applied force with a sensitivity of 1 g and a sampling rate of 50 Hz. Any force on the catheter tip causes corresponding microdeformation of the elastic polymer. The optical fibres transmit an infrared laser light which is reflected by fibre Bragg gratings with a changed wave-
length due to the microdeformation of the elastic polymer – the changes in wavelength being proportional to the CF applied [33, 34]. The SmartTouch™ catheter is a 3.5 mm open irrigated-tip ablation catheter. The force-sensing capability of this catheter is based on the electromagnetic location technology used in the CARTO 3D mapping System (Biosense Webster, Inc., MA, USA). The catheter tip electrode is mounted on a precision spring that permits a small amount of electrode deflection. A transmitter coil that is coupled to the tip electrode, distal to the spring, emits a location reference signal. Three magnetic location sensor coils placed at the proximal end of the spring detect micromovements of the transmitter coil, representing movement of the tip electrode on the spring. The system senses the location information of the sensor and calculates the respective force based on the known spring characteristics. The movements are sampled at 20 Hz and calibrated to produce a CF reading that is averaged over 1 second and accurate within 1 g. Of note, the catheter is fully integrated within the electroanatomical mapping system [35]. The EnSite Contact VeriSense™ System uses the principle of electrical coupling as the local measure of impedance (unlike the impedance normally used, which is a global measure between the catheter tip and a body-surface electrode) specific to the catheter tip-to-tissue interface through a three-terminal circuit model. The complex local coupling information is then provided as ECI (electrical coupling index) units within the three-dimensional cardiac mapping system using a real-time curve, a contact meter and an adaptive colour-coded beacon as the tip of the ablation catheter. This technology requires: scaling to the individual patient by acquisition of noncontact ECI baseline values, while the catheter rests free in the left atrium (LA) body; definition of the patient-specific noncontact/contact threshold 15 ECI units above the noncontact baseline; and acquisition of an upper safety indication while firmly pressing the catheter against the posterior LA wall. This scaling needs to be repeated every 30 minutes to adapt to shifts in the baseline values during the procedure [36].

IntelliSense® Fine Force Technology and EnSite Contact VeriSense™

Early in-vitro reports on the actual remote robotic catheter control system were able to show precise navigation and control of the remote catheter with the ability to reach a targeted endocardial site accurately and rapidly [37]. Thereafter, in-vivo studies followed and provided the basis for the above-mentioned CF system [31, 38, 39]. An in-vitro study examined the direct impact of catheter CF on lesion formation by using the remote robotic catheter control system [40]. The authors used intracardiac ultrasound (ICE) and fluoroscopy for validation of catheter tip / tissue contact and CF in twelve dogs undergoing irrigated-tip atrial ablation at 15 W for 30 seconds. Two different validation protocols were applied. In the first protocol, catheter tip / tissue contact as visualised by use of ICE/fluoroscopy was defined as “no contact”, “minimal contact”, “consistent contact throughout cardiac and respiratory cycles” and “tissue tenting”. Measured corresponding CF values, to which the operator was blinded, were correlated with each condition. In the second protocol, catheter tip / tissue contact was generated by 2 g, 2–10 g, 10–20 g and 20 g of CF, and catheter tip / tissue contact was subsequently graded as above. Importantly, catheter tip / tissue surface angles were considered perpendicular if the angle between the tissue surface and the catheter was >45°. In addition, the impact of catheter tip / tissue contact on 3D-electroanatomical mapping and contact-dependency of lesion size were assessed. In summary, the authors concluded that, in accordance to earlier reports, both mapping and ablation with this robotic sheath guidance system are critically dependent on generated CF and they suggested further that ablative lesion size may be optimised by the application of 10–20 g of CF, whereas mapping requires application of lower CF to avoid image distortions and increases in chamber volumes [40]. A more recently published in-vitro analysis using the same system was able to confirm these findings, observing a correlation between transmurality and CF, with an increased risk of steam pop and char formation when applied with ≥40 g, whereas a CF between 20–30 g and a power setting of 40 W appeared to be associated with transmurality by preserving safety [32]. One major limitation of this technology is that it does not provide feedback on different directional forces applied to the catheter (i.e. angle-dependent CF values), which is why visual fluoroscopic information remains crucial. As the authors point out, a non-perpendicular catheter orientation and force application might go along with contact loss and impair the measurement of the generated CF. Furthermore, parasitic frictional forces have to be overcome during every catheter placement [40]. Feasibility in human validation and use of the ECI using the EnSite Contact™ system have been assessed in two main studies with patients suffering from atrial fibrillation (AF). While the operators had to
place the ablation catheter in the LA in different areas of unambiguous “qualities” of contact as determined by fluoroscopy, tactile feedback, unipolar and bipolar EGM recordings measurement and validation of the CF surrogate ECI were performed [41]. The same group recently described a prospective randomised pilot study, which demonstrated an added value of ECI for lesion creation as measured as higher rates of pulmonary vein isolation (PVI) after anatomical encircling [36]. However, ECI and the nature of relative changes during tissue contact are not fully understood and remain more complicated than established measures for CF. Furthermore, it lacks the precise distinction between different levels of contact as well as short instantaneous changes, e.g., during cardiac cycle and respiratory movements [41].

TactiCath® and SmartTouch™

An ex-vivo porcine model to determine the importance of CF during irrigated-tip RF ablation has been described [33, 42, 43]. Basically, it could be demonstrated that CF is a main determinant of tissue temperature and lesion size, when controlled for power and duration of open-irrigated RF energy delivery. Largest lesions were obtained using a high fixed power and CF (30 W / 60 g; 12 mm wide and 8.1 mm deep). The results showed that higher CF was associated with a higher incidence of thrombus formation and/or steam pops. Of note, in contrast to experiences gathered from closed-irrigation ablation systems, this study found that the impedance drop during RF energy delivery was not predictive of the degree of CF, whereas other works showed that the initial impedance at the start of the application, as well as the impedance drop in the first 5 seconds, correlate well with CF, suggesting the potential use of these parameters when direct CF measurements are not available [43–46].

The first clinical study investigating device and procedure-related safety (12 months of follow-up) with the TactiCath® system for the RF ablation of rightsided supraventricular tachycardias (SVTs) and AF was the TOCCATA study [47]. Two patient groups with various atrial arrhythmias were enrolled: a rightsided SVT group (n = 43) including patients with a confirmed diagnosis of atrioventricular-nodal reentry tachycardia, Wolff-Parkinson-White syndrome, atrial tachycardia and cavo-tricuspid isthmus-dependent atrial flutter and a left-sided AF group (n = 34) including patients with confirmed paroxysmal AF. The TOCCATA-study protocol required the CF values to be concealed from the investigators (all experienced operators) during mapping in order to minimise bias on the force being applied, whereas CF data were available during the ablation phase. Based on earlier experiences, high CF values in the AF group were defined as increases to >100 g for over 200 ms and, since the study was specifically designed for the assessment of safety, prespecified safety rates were derived from the literature (estimated incidence of serious adverse events for right-sided SVT at 11.4%, for patients with AF at 16.8%) [48]. The authors concluded that the safety profile was comparable to conventional irrigated-tip RF catheters and the incidence of serious adverse events in both groups clearly below the prespecified rates (2% and 12%, respectively). The study further highlighted a marked inter- and intraoperator variability during the assessment of CF values and that high CF values naturally may occur at any moment during catheter manipulation, regardless of whether one ablates or not. As a matter of fact, the one perforation event in the TOCCATA-study was shown to be preceded by a very high transient force during catheter manipulation and not during ablation. The high force of 137 g was then followed by a sudden decrease in force. Such a CF pattern typically occurs at and immediately after a perforation, as has been described in a recent analysis of forces required to perforate mechanically and transmurally the walls of the four cardiac chambers of 50–60 kg pigs [48]. Further important observations by the same authors were: (a) perforation forces are significantly lower in the right atrium and right ventricle (RV) (301 ± 117 g, 297 ± 82 g, respectively) as compared with the left atrium (LA) and left ventricle (LV) (417 ± 167 g, 457 ± 204 g, respectively) without any differences between the respective ventricles and atria; (b) perforation forces are significantly lower through transmural RA free wall RF lesion than through healthy, unablated RA tissue (372 ± 79 g vs 301 ± 117 g, p <0.0002); and (c) cardiac perforation with a catheter within a sheath is more rapid and easier than without the use of a sheath, the latter preventing the distal catheter shaft from buckling and dissipating the CF delivered by the operator proximally. Of note, the minimum CF for perforation in healthy tissue without a sheath was 131 g and lowest in the RA, while 159 g in the LA, 168 g in the RV and 227 g in the LV [48].

Such observations clearly suggest that the avoidance of CF values exceeding 100 g at any time during the procedure is crucial. Moreover, CF should be kept at low levels in the vicinity of recently ablated sites, where the tissue is structurally weakened [47, 48]. Finally, TOCCATA was the first clinical study to con-
firm that knowledge of the CF during the entire procedure may clearly improve safety aspects and increases the operators’ awareness of high-risk situations. The clinical outcome of the AF group of the TOCCATA study population was investigated further by assessing the relationship between CF and clinical recurrences during the 12-months’ follow-up. Acute pulmonary vein isolation was achieved in 100% of the patients, yet all patients treated with an average CF of <10 g (five of five patients) experienced AF recurrences, whereas 80% of the patients treated with an average CF of >20 g (8 of 10 patients) had none [49]. Of note, fluoroscopy and total RF times were higher in the patient group with AF recurrences, possibly suggesting difficulties with stable catheter positioning as a reason for low CF, all the more so as the operators were not blinded to CF in the ablation part and thus actually would have wanted to achieve higher CFs but had difficulties doing so. Apart from the absolute and average CF value during RF application, time-dependent evolution of CF quantified as the force-time integral (FTI or area under the CF curve, in gram-seconds, gs) proved to correlate linearly with lesion size [30, 49]. The findings of this one-arm prospective study underlined once more the importance of a real-time measurement of CF during RF, which allows the operator to base his/her ablation strategy on causally interrelated data, and thus compensate for low CF due to anatomical and/or technical factors by varying either RF power and/or duration or repositioning the catheter to improve contact. In this context, important further evidence about the relationship between CF measurement during RF application (EFFICAS I study) and the incidence of isolation gaps in the pulmonary vein (PV), and about areas of intrinsically good, poor, and excessive contact at the PV antrum, has been gathered through recently published studies [34, 35, 45, 50–52]. The findings of the EFFICAS I study, where invasive electrophysiological assessment of conduction gaps at PVI ablation sites was performed 3 months after the index ablation procedure, showed a strong correlation between the minimum CF and minimum FTI values and the subsequent gap formation. These and other authors suggested that CF stability is required before ablation in order to minimise the risk of unstable contact and ineffective lesion formation, particularly in the left anterior segment, and suggested a target CF of 20 g, albeit with an absolute minimum CF of 10 g and an absolute minimum FTI of 400 gs [34, 53]. Last but not least, safety and efficacy results from the SMART-AF trial, a prospective, nonrandomised study of 172 enrolled patients with paroxysmal AF, have recently been presented. Comparable to previous studies assessing safety, the authors reported a 12-month success rate of 72%. Furthermore, increased percent of time with physician-targeted CF correlated with increased freedom from arrhythmia recurrence, with 84.4% of subjects being arrhythmia-free at 12 months when the CF was within the targeted range >82% of the time [54].

Regardless of the system, improving catheter stability as well as contact, and achieving higher CF for RF ablation of AF may also depend upon other parameters, such as choosing general anaesthesia or additional tools such as intracardiac ultrasound technology or steerable sheaths. As a matter of fact, higher clinical success along with comparable complication rates have been associated with the use of a manually controlled steerable sheath for catheter navigation in RF for AF [55]. Furthermore, administration of adenosine for the assessment of dormant conduction may help the operator to target eventual gaps [56, 57].

Catheter contact force in mapping and ablation of ventricular tachycardia

Parameters allowing control of lesion size as well as procedural safety in left atrial procedures, have very recently proved their applicability for endo- and epicardial ventricular mapping and ablation. Ventricular tachycardia mapping can be challenging, but is also crucial for successful ablation and subsequent clinical outcome. Patients frequently do not tolerate sustained arrhythmias, rendering complete mapping difficult or impossible. Furthermore, the optimal approach between an antegrade, transseptal and retrograde transaortic approach or a combination of both and/or the use of a steerable sheath is often unclear for the creation of a meaningful electro-anatomical map.

To date, two studies have addressed these issues with largely congruent results [58, 59]. Mizuno et al. were the first to assess the use of CF-sensing catheters in left ventricular tachycardia mapping in humans [58]. They compared a combined antegrade, transseptal approach (with a steerable sheath) and a retrograde, transaortic mapping strategy with a retrograde-only approach in 27 chambers (13 LV, 6 RV, 8 epicardial) of 17 different patients (under general anaesthesia). They divided all acquired mapping points into two groups according to the presence of positive CF throughout a complete cardiac cycle (i.e. including during diastole) and evaluated the value of surrogate parameters such as fluoroscopy, electrogram amplitude and local impedance for predicting tissue con-
tact [58]. Once more, these surrogate parameters turned out to be unsatisfactory for monitoring tissue contact, since they led to the acquisition of points with an unpredictable CF variability and with a poor contact, which emphasises the importance of awareness of a minimum CF to achieve a stable tissue contact throughout the whole cardiac cycle: estimated to be 8 g for left ventricular endocardial and epicardial mapping, and 9 g for the right. They also showed that the combined approach to the left ventricle was superior in terms of clinical outcomes and that poorer CF values during mapping of the anterior and basal septal walls of the left ventricle with the retrograde approach may be related to the requirement of two curves in the mapping catheter, one in the aortic arch and the second in the left ventricle, thus possibly reducing tissue contact [58]. Tilz et al. recently added more evidence in line with these observations by comparing the impact of antegrade-transseptal with retrograde-transaortic left ventricular mapping on catheter stability and CF, and assessing the value of surrogate parameters for tissue contact [59]. Lesion formation after RF ablation on the right and left ventricular endo- and epicardium has been investigated in a sheep model using a standard irrigated-tip catheter versus a CF sensing catheter [60]. Acute lesion dimensions were assessed after RF ablation (160 endocardial and 160 epicardial RF applications) with 30 W for 60 seconds when either catheter/tissue contact (based on fluoroscopy / tactile feedback / EGM amplitude) was considered to be good with the standard irrigated-tip catheter or when CF was higher than 10 g as measured with the CF-sensing catheter. This analysis showed that conventional surrogates of good catheter-tissue contact such as fluoroscopy, tactile feedback and EGM amplitude did not result in endocardial lesion formation in 22% of RF applications, whereas lesion formation was absent in the CF-sensing group only when RF was applied with a CF lower than 10 g together with a FTI of less than 500 gs, perfectly in line with results from the TOCCATA study. However, such absolute values of CF and FTI do not seem to be directly transferable for predicting lesion size in epicardial RF applications, where FTI was, indeed, twice lower than in the endocardium, but lesion volume was significantly larger; this was most probably due to absence of circulating blood in the pericardial space and, therefore, lack of convective cooling. Furthermore, presence of epicardial fat has been shown to have a considerable effect on lesion formation [61], and last but not least, the catheter has a more parallel orientation on the epicardial surface and therefore the applied CF has a greater lateral than axial component, thus altering lesion geometry. These important novel insights have recently been reported to be very helpful for successful CF-guided endocardial and epicardial ablation of ventricular tachycardia [62, 63]. Of note, the added ventricular wall thickness may require deeper, larger lesions usually achieved by a combination of higher power and higher CF. With such parameters, the risk of pop formation is likely to be higher, although perforation may be a less likely consequence compared with the thin walled atria. The body of evidence supporting the security and efficacy of specific power and CF parameters for RF ablation in the ventricles is currently limited, precluding specific recommendations.

Conclusion

Real-time catheter contact force measurement technology has provided crucial insights into technical and biophysical aspects of catheter-based arrhythmia treatment using RF energy. Optimal contact force is fundamental for the acquisition of reliable mapping information and achievement of sustained ablation lesions. The choice between different CF sensing technologies, the type of patient sedation or anaesthesia, different approaches to the cardiac chamber of interest and the knowledge of its anatomy as well as the use of steerable sheaths guaranteeing better catheter stability should be made carefully, with the aim of assuring stable and optimal catheter contact force values and maximising the probability of effective and safe lesion formation and sustained ablation success. Further studies will provide more experience with CF-assisted ablation and hopefully lead to further improvement in the outcomes of RF ablation for cardiac arrhythmias.

Funding / potential competing interests

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References
- The full list of references is attached to the online version at www.cardiovascmed.ch
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Einleitung


ST-Hebungen

Elektrokardiographische ST-Hebungen sind nicht ACS-spezifisch. So hatten beispielsweise 123 Patienten mit Thoraxschmerzen und einer ST-Hebung ≥0,1 mV nur in 48% der Fälle tatsächlich einen Herz-
infarkt [6]. Die übrigen falsch-positiven Patienten zeigten Linksschenkelblockbilder oder es bestand eine linksventrikuläre Hypertrophie. Ein STEMI ist in aktuellen Richtlinien [4] definiert als akute Hebungen der ST-Strecke (am J-Punkt) in mindestens zwei zueinander passenden Ableitungen von ≥0,1 mV. In den Ableitungen V2–V3 gelten andere diagnostische Grenzwerte: ≥0,25 mV bei Männern <40 Jahren, ≥0,2 mV bei Männern <40 Jahren und ≥0,15 mV bei Frauen. Diese Kriterien gelten nicht beim Linksschenkelblock (LSB) und der linksventrikulären Hypertrophie. Eine isolierte ST-Hebung (auch <0,1 mV) in aVL oder I kann diagnostisch für einen akuten Verschluss einer Seitenwandarterie (z.B. Diagonalast) sein. Bei inferioren Infarkten wird empfohlen, zusätzlich rechtspräkordiale Ableitungen (V₅R und V₆R) zu erfassen, um eine (prognostisch ungünstige [7]) Rechtsherzbelastung zu diagnostizieren (diagnostische Grenzwerte: >0,05 mV bzw. >0,1 mV bei Männern <40 Jahren). Zudem können zusätzliche (posteriore) Thoraxwandaableitungen V₇–V₉ helfen, das Ausmass der akuten Ischämie abzuschätzen (z.B. bei Okklusion eines dominanten Ramus circumflexus [RCX] oder einer dominanten Arteria coronaria dextra [RCA]).


### Tabelle 1: Repolarisationsstörungen ohne ACS, exemplarische Auflistung ohne Anspruch auf Vollständigkeit.

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<th>Tabelle 1: Repolarisationsstörungen ohne ACS, exemplarische Auflistung ohne Anspruch auf Vollständigkeit.</th>
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<td>Normalvarianten, z.B. frühe Repolarisation</td>
</tr>
<tr>
<td>Blockbilder</td>
</tr>
<tr>
<td>Linksventrikuläre Hypertrophie</td>
</tr>
<tr>
<td>Hypertrophe Kardiomyopathie</td>
</tr>
<tr>
<td>Ventrikuläre Schrittmacherstimulation</td>
</tr>
<tr>
<td><strong>ST-Senkungen</strong></td>
</tr>
<tr>
<td>Blockbilder</td>
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<tr>
<td>Linksventrikuläre Hypertrophie</td>
</tr>
<tr>
<td>Hypertrophe Kardiomyopathie</td>
</tr>
<tr>
<td>Chronische Ischämie</td>
</tr>
<tr>
<td>Ventrikuläre Schrittmacherstimulation</td>
</tr>
<tr>
<td><strong>Negative T-Wellen</strong></td>
</tr>
<tr>
<td>Normalvarianten, z.B. Frauen, Jugendliche</td>
</tr>
<tr>
<td>Stattgebahter Herzinfarkt</td>
</tr>
<tr>
<td>Chronische Ischämie</td>
</tr>
<tr>
<td>Kardiomyopathien</td>
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<tr>
<td>Blockbilder</td>
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<tr>
<td>Linksventrikuläre Hypertrophie</td>
</tr>
<tr>
<td>Ventrikuläre Schrittmacherstimulation</td>
</tr>
<tr>
<td><strong>Prominente T-Wellen</strong></td>
</tr>
<tr>
<td>Normalvarianten, z.B. frühe Repolarisation</td>
</tr>
<tr>
<td>Akute intrakranielle Prozesse (Stroke, Subarachnoidalblutung)</td>
</tr>
</tbody>
</table>

### ST-Senkungen
EINV
t AR TICL E
165
tis, Lungenembolie, Elektrolytstörungen, hypertensive
Krise, Digoxinmedikation usw.) ist breit.

T-Inversionen

II typisch für eine proximale RIVA-Läsion (z.B. vor dem Abgang des ersten Diagonalastes).


und aVF abgeleitet, während bei der Tako-Tsubo-Kardiomyopathie T-Inversion häufig gleichzeitig in fast allen Ableitungen beobachtet werden können (Abb. 3).

Atypische EKG-Präsentationen

Verschiedene klinische Szenarien mit atypischen EKG-Präsentationen sind heutzutage bekannt und bedürfen vermehrter Aufmerksamkeit in der akuten Präsentation.

ST-Hebungen in aVR


Dieses spezielle EKG-Muster (Abb. 4) zeigt nur bei 23% der Fälle einer hochgradige Hauptstammstenose bzw. ein angiographisches Hauptstammäquivalent, während bei 26% der Fälle keine signifikante koronare Herzkrankheit vorlag [17]. Der positiv-prädiktive Wert konnte auch nach Ausschluss von Patienten mit intraventrikulären Leitungstörungen, linksventrikulärer Hypertrophie oder dynamischen Veränderungen nicht verbessert werden.

ST-Senkungen in V1–V3

Akute ST-Senkungen in V1–V3 können spiegelbildlich betrachtet die typische ST-Hebungsmorphologie zeigen. Besonders bei terminal positiver T-Welle kann dies für eine posteriore Ischämie hinweisend sein. Hier wird zur Bestätigung empfohlen, in zusätzlichen (posterioren) Ableitungen V1–V3 ST-Hebungen >0,05 mV (oder 20,1 mV) zu suchen.

Ischämische Symptome ohne diagnostische EKG-Veränderungen


Neuaufgetretener Linksschenkelblock (LSB)


Bekannter Linksschenkelblock / ventrikuläre Schrittmacherstimulation


Telemedizinische EKG-Übertragungen in der Akutmedizin (Prehospital-ECG)

Neben verschiedenen präklinischen Systemen zur EKG-Übertragung vom Rettungsfahrzeug zu stationären Institutionen (Notfallstationen, Herzkathe-telabore, Einsatzzentralen, Dienstärzte usw.) sind auch EKG-Übertragungen auf Smartphones zunehmend verbreitet (sogenannte «Prehospital-ECG»). Der Einsatz eines Prehospital-ECG scheint beneficial, so konnte retrospektiv an über 150.000 ACS-Patienten gezeigt werden, dass Patienten mit einem präklinischen 12-Ableitungs-EKG deutlich eher einer Reperfusionstherapie zugeführt wurden (OR 1,7; 95%-CI 1,63–1,78). Der Einsatz eines Prehospital-ECG hatte einen signifikanten Einfluss auf die 30-Tages-Mortalität sowohl bei STEMI-Patienten (8,6% vs. 11,4%; OR 0,94; 95%-CI 0,90–0,98) als auch bei NSTEMI-Patienten.

Im Falle von ausserklinisch erfolgreich reanimierten Patienten nach Kreislaufstillstand wird heutzutage bei STEMI-Diagnose eine unverzügliche Akut-PCI empfohlen (präklinische Direktaktivierung sinnvoll), bei NSTEMI-Patienten soll eine Akut-PCI beschleunigt (innerhalb von 2 Stunden) durchgeführt werden (präklinische Direktaktivierung fraglich/situationell), und bei unklarer Ursache für den Kreislaufstillstand macht eine kurze differentialdiagnostische Evaluation im Setting einer Notfallstation/Schockraum Sinn [26] (präklinische Direktaktivierung meist wenig sinnvoll). Das Prehospital-ECG kann generell helfen, die entsprechenden adäquaten Versorgungselemente der Rettungskette zeitgerecht zu alarmieren und in Bereitschaft zu versetzen.

Schlussfolgerungen


Finanzierung/Interessenkonflikte

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Literatur

Die vollständige nummerierte Literaturliste finden Sie an der Online-Version angehängt unter www.cardiovascmed.ch.

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REFERENCES

Feasibility, bleeding events and impact on door-to-balloon times

Switching from femoral to radial access for coronary angiography in ACS

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Department of Cardiology, Triemlispital Zurich, Switzerland

Summary

Background: Transradial access (TRA) for coronary angiography (CA) is thought to be superior to the transfemoral approach (TFA) in patients presenting with an acute coronary syndrome (ACS) regarding access site complications and bleeding events. As an institution that primarily uses TFA for CA, we switched to TRA during the year 2012. The aim of this study was to look for differences in bleeding events, procedure times, contrast use in ACS patients and door-to-balloon (dtb) times in STEMI patients comparing the TRA and TFA, respectively.

Methods/results: A total of 789 ACS patients underwent CA in 2012. Of these, 502 patients had the TFA and 287 patients the TRA for CA. The overall bleeding rate was 14.1% for TFA and 5.3% for TRA (p <0.01) using the BARC (bleeding academic research consortium) criteria. Access site-related bleeding events were 10.5% in the TFA group and 3.9% in the TRA group (p = 0.01). There were no differences regarding procedure times or contrast use between the two groups. In a multivariate analysis, gender, age, Gp IIb/IIIa use and access site were independent predictors of bleeding events. Of the 789 patients, 428 were STEMI patients. Dtb time was 106 ± 100 minutes (including transfer patients). There was no difference regarding dtb time between the TRA and the TFA group.

Conclusion: For experienced “femoral operators”, a switch to the radial access site is feasible and safe. There is no increase in dtb time, fluoroscopy time or contrast use, but a significant decrease in bleeding events with the radial approach in patients presenting with ACS.

Key words: radial access; acute coronary syndrome; access site bleeding; bleeding risk; door-to-balloon time

Introduction

The transradial approach (TRA) for coronary angiography (CA) was initially described by Campeau [1] in 1989 and for percutaneous coronary intervention (PCI) by Kiemeneij and Laarman [2] in the early 90s. Although the technique was rapidly adopted by a few groups in Europe, Canada, the United States and Asia, widespread use has not occurred. The obvious advantage of the radial artery compared with the femoral artery is the superficiality of the vessel with no adjacent structures susceptible to be damaged during percutaneous procedures. Hence, despite the use of aggressive antithrombotic regimens required for PCI, the artery is readily compressible, and introducer sheaths can be immediately removed upon completion of procedures. Haemostasis can be achieved safely and rapidly using simple compressive devices. Two meta-analyses reviewing randomised trials comparing TRA with the traditional transfemoral approach (TFA) for diagnostic coronary angiography or interventions estimated a 73% reduction in the risk of access site-related bleeding and an 80% risk reduction of major bleeding [3, 4]. These benefits are associated with earlier ambulation, increased patient comfort, and reduced duration of hospitalisation with substantial cost containment. However, the smaller calibre of the radial artery as well as the greater anatomical variability of its vascular course and distribution in the arm has been associated with a steep learning curve resulting in an increase in procedural failure and a higher rate of cross-over to femoral route [4]. Two recent large randomised trials comparing the two access sites in acute coronary syndrome (ACS) patients revealed less access site related bleeding in the subgroup with ST elevation myocardial infarction (STEMI) [5] with a reduction of cardiac mortality in one trial [6]. In the current ESC guidelines for STEMI treatment, TRA is the preferred access route in experienced centres [7] and there is a new consensus document on how to introduce TRA in a primarily femoral access center [8]. In 2012 we introduced TRA for coronary angiography and percutaneous coronary intervention (PCI) in ACS patients as the new standard approach at our centre, in accordance with the current guidelines. In this study we compared TFA to TRA in troponin-positive ACS patients regarding inhospital bleeding events.
door-to-balloon (dtb) times, contrast use and total fluoroscopy times.

Methods

This study was a single centre prospective registry study. All patients underwent diagnostic coronary angiography for a troponin-positive ACS. TRA was encouraged and operators switched to TRA according to a current consensus document [8] (first in elective patients, then stable ACS patients and finally in STEMI patients). All involved operators were using the TFA as a default approach for CA before this study. Five operators had >5 years’ experience in interventional cardiology; one operator had 2 years of experience in interventional cardiology.

All patients received an unfractionated heparin dose of at least 5000 IU i.v. preprocedure and a bolus of 300 mg aspirin i.v. if they were not already on aspirin treatment. Activated clotting time (ACT) was maintained >250 sec during the procedure, although ACT was not measured routinely. The use of a Gp IIb/IIIa antagonist was left to the operator. All patients received dual antiplatelet treatment with aspirin and clopidogrel, ticagrelor or prasugrel with a standard loading dose (600 mg for clopidogrel, 180 mg for ticagrelor and 60 mg for prasugrel). Clinical variables were collected from the individual patients’ charts; coronary angiography and coronary intervention details were collected from the coronary intervention report and the procedure protocol.

In the STEMI subgroup, door-to-balloon time was defined as first medical contact to TIMI III flow in the culprit vessel. If there was spontaneous TIMI III flow, the time of (successful) arterial puncture (radial or femoral) was used to calculate door to balloon time. The primary endpoint was (in hospital) access site-related bleeding. Secondary endpoints were total bleeding events (in hospital), total procedure/fluoroscopy times and dtb times (only STEMI patients), compared between the two different access sites. Bleeding events were defined according to the bleeding academic research consortium definition (BARC) [9]. All patients gave written informed consent for the study and the study was approved by the local ethics committee.

Statistics

Baseline characteristics of the patients are summarised as mean ± standard deviation (SD) for continuous variables and number (percentage) for categorical variables. The Student t test was computed for bivariate analyses. To look for independent risk factors for bleeding events we computed a multivariate analysis using nominal logistic regression. Only variables with p-values <0.1 in the univariate analysis were included in the multivariate analysis. Risk factors for bleeding events analysed in the univariate analysis were: gender, age, access route for coronary angiography, diabetes, renal failure (defined as creatinine clearance <60 ml/min), body mass index and use of Gp IIb/IIIa antagonists. A two-tailed p-value <0.05 was established as the level of statistical significance for all tests. Statistical analyses were performed using Jmp 11.0 (SAS).

Results

In 2012, 789 patients underwent coronary angiography as a result of a troponin-positive ACS at our institution (mean age 63.9 ± 13.0 years; 24.6% women). TRA rate for ACS patients was around 10% in January 2012, increasing to over 60% in December 2012. A total of 502 patients had the TFA for coronary angiography compared with 287 patients with a TRA in 2012. Patients in the TFA group were older compared with the TRA group (64.9 ± 12.6 vs 62.2 ± 13.5; p <0.01) and there were more STEMI patients in the TFA group than in the TRA group (59.7% vs 44.6%; p <0.01) (table 1). The periprocedural characteristics were comparable between the two groups except for number of vessels diseased (average of 2.0 ± 1.0 vessel disease in the TFA group vs 1.8 ± 0.9 in the TRA group; p = 0.01) and periprocedural use of a Gp IIb/IIIa antag-

Table 1: Baseline characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Radial (n = 285)</th>
<th>Femoral (n = 504)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>62.2 ± 13.5</td>
<td>64.9 ± 12.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Gender (male; %)</td>
<td>74.4</td>
<td>77.2</td>
<td>NS</td>
</tr>
<tr>
<td>STEMI (%)</td>
<td>44.6</td>
<td>59.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>16.5</td>
<td>14.9</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>51.6</td>
<td>52.6</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>34.4</td>
<td>31.1</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine (μmol/l)</td>
<td>79.1 ± 23.5</td>
<td>86.4 ± 56.3</td>
<td>NS</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>27.2 ± 4.4</td>
<td>27.0 ± 9.3</td>
<td>NS</td>
</tr>
<tr>
<td>Previous stroke (%)</td>
<td>4.8</td>
<td>3.8</td>
<td>NS</td>
</tr>
<tr>
<td>Previous myocardial infarction (%)</td>
<td>15.4</td>
<td>19.0</td>
<td>NS</td>
</tr>
<tr>
<td>Previous CABG (%)</td>
<td>1.8</td>
<td>4.4</td>
<td>0.05</td>
</tr>
<tr>
<td>Previous PCI (%)</td>
<td>14.7</td>
<td>17.5</td>
<td>NS</td>
</tr>
<tr>
<td>PVD (%)</td>
<td>2.5</td>
<td>5.4</td>
<td>0.05</td>
</tr>
<tr>
<td>OAC (%)</td>
<td>2.8</td>
<td>3.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

CABG = coronary artery bypass grafting; NS = not significant; OAC = oral anticoagulant treatment; PCI = percutaneous coronary intervention; PVD = peripheral vascular disease; STEMI = ST elevation myocardial infarction.
onist (33.9% vs 14.4%; p < 0.01; table 2). Gp IIb/IIIa use was significantly less in the non-STEMI group (19.2% in TFA group vs 5.1% in TRA group; p < 0.01) compared with the STEMI group (44.2% in TFA group vs 26.8% in TRA group; p < 0.01). There were no differences regarding contrast use or fluoroscopy times between the TFA and the TRA group. Crossover rate from the TRA to the TFA was 8.1%. All swaps from radial to femoral access were due to technical access problems (e.g., radial artery size, radial artery anatomy, short ascending aorta, etc.) and not due to the complexity of the procedure. The overall bleeding rate was 14.3% for the TFA and 5.3% for the TRA group (p < 0.01) using the BARC bleeding criteria. Access site-related bleeding rates were 10.5% and 3.9%, respectively (p = 0.01). The strongest predictor of access site-related bleeding was the use of a Gp IIb/IIIa antagonist. Among patients without Gp IIb/IIIa use, there was still a trend towards a lower access site-related bleeding rate in the TRA group (table 3).

In a multivariate analysis including only variables with p values < 0.1 in univariate analysis of bleeding events, gender (p = 0.02), age (p = 0.03), Gp IIb/IIIa use (p < 0.001) and access site (p = 0.03) were independent predictors of bleeding events (table 4). Inhospital mortality rate was 4.4% overall, 5.9% in the TFA group and 1.8% in the TRA group (p = 0.001). A total of 428 of the 789 patients were STEMI patients. Average dtb time was 106 ± 100 minutes. About two-thirds of the STEMI patients had been transferred from non-PCI capable hospitals. There was no significant difference between the TFA compared to the TRA group regarding dtb times (table 2).

### Discussion

Our data demonstrate that it is safe to switch from the TFA to the TRA in ACS patients without increasing dtb times, fluoroscopy times or contrast use when the technique is introduced according to a current consensus document. Additionally, the risk of access site-related bleeding is smaller with the TRA, especially in patients receiving Gp IIb/IIIa antagonists. Coronary angiography and finally PCI through the radial approach started in the late 80s and early 90s but only recently has the reduced access site-related bleeding events in ACS patients compared with the TFA been documented in large studies [1–6]. One recent large randomised study showed a reduction in access site bleeding and a reduction in cardiovascular mortality with TRA in STEMI patients [6]. Another large randomised trial did not show any mortality benefit when comparing the two approaches in ACS patients but there was a reduction in access site-related bleeding (although only if the ACUITY [10] bleeding criteria were used), especially in TRA experienced centres [5]. We used the BARC [9] bleeding criteria in our study, which are more sensitive than the TIMI or ACUITY criteria. The rates of bleeding events were therefore slightly higher in our study than in these randomised trials. Nevertheless, access site-related bleeding events were lower in the TRA group in

### Table 2: Periprocedural characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Radial (n = 285)</th>
<th>Femoral (n = 504)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total fluoroscopy time (min)</td>
<td>11.2 ± 6.1</td>
<td>12.1 ± 8.8</td>
<td>NS</td>
</tr>
<tr>
<td>Total contrast used (ml)</td>
<td>238 ± 75</td>
<td>241 ± 84</td>
<td>NS</td>
</tr>
<tr>
<td>Door-to-balloon time (STEMI patients only)</td>
<td>111.5 ± 123.0</td>
<td>104.0 ± 90.4</td>
<td>NS</td>
</tr>
<tr>
<td>Number of guides used</td>
<td>1.1 ± 0.4</td>
<td>1.1 ± 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Total stent length (mm)</td>
<td>28 ± 17</td>
<td>31 ± 20</td>
<td>0.06</td>
</tr>
<tr>
<td>Access site crossover</td>
<td>8.1%</td>
<td>0%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>X-vessel disease</td>
<td>1.8 ± 0.9</td>
<td>2.0 ± 1.0</td>
<td>0.01</td>
</tr>
<tr>
<td>Gp IIb/IIIa use (%)</td>
<td>14.4</td>
<td>33.9</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

NS = not significant; STEMI = ST segment elevation myocardial infarction

### Table 3: Bleeding events.

<table>
<thead>
<tr>
<th></th>
<th>Radial (n = 285)</th>
<th>Femoral (n = 504)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any bleeding (%)</td>
<td>5.3</td>
<td>14.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Access site bleeding (%)</td>
<td>3.9</td>
<td>10.5</td>
<td>0.01</td>
</tr>
<tr>
<td>Any bleeding without Gp IIb/IIIa use (%)</td>
<td>4.1</td>
<td>8.7</td>
<td>0.03</td>
</tr>
<tr>
<td>Access site bleeding without Gp IIb/IIIa use (%)</td>
<td>2.9</td>
<td>6.0</td>
<td>0.07</td>
</tr>
<tr>
<td>Bleeding according to BARC criteria (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BARC 2</td>
<td>4.2</td>
<td>9.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>BARC 3a</td>
<td>0</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>BARC 3b</td>
<td>1.1</td>
<td>2.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>BARC 5</td>
<td>0</td>
<td>0.4</td>
<td></td>
</tr>
</tbody>
</table>

BARC = bleeding academic research consortium

### Table 4: Multivariate analysis regarding risk factors for bleeding events.

<table>
<thead>
<tr>
<th></th>
<th>95% confidence interval*</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male)</td>
<td>-0.58 to -0.05</td>
<td>0.02</td>
</tr>
<tr>
<td>(Lower) age</td>
<td>-0.04 to -0.005</td>
<td>0.02</td>
</tr>
<tr>
<td>Access route for coronary angiography (femoral)</td>
<td>0.04 to 0.66</td>
<td>0.03</td>
</tr>
<tr>
<td>Diabetes</td>
<td>-0.70 to 0.08</td>
<td>NS</td>
</tr>
<tr>
<td>Renal failure</td>
<td>-0.20 to 0.46</td>
<td>NS</td>
</tr>
<tr>
<td>Gp IIb/IIIa use (%)</td>
<td>0.37 to 0.87</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

NS = not significant

Only variables with p values < 0.1 in the univariate analysis were included in the multivariate analysis. Risk factors for bleeding events analysed in the univariate analysis were: gender, age, access route for coronary angiography, diabetes, renal failure (defined as creatinine clearance < 60 ml/min), Body Mass Index and use of Gp IIb/IIIa antagonists.

* Values < 0 indicate protection regarding bleeding events, values > 0 indicate higher bleeding risk
our registry as well. Using multivariate analysis, conventional risk factors for bleeding events like Body Mass Index, renal function and diabetes mellitus were not associated with bleeding events. One possibility is that our sample size was too small to detect an effect of these weak risk factors for bleeding in ACS patients. On the other hand the strongest predictor for a bleeding event was the use of a Gp IIb/IIIa antagonist. Additional independent risk factors for bleeding events were gender, age and access site for coronary angiography.

Crossover rates from the TRA to the TFA were 8.1% in our study, altogether comparable to previous work (7.6%–9.6%; [5, 6]).

A current consensus document recommends the introduction of the TRA in a stepwise manner (diagnostic coronary angiography in elective patients first, then PCI in elective patients followed by PCI in non-STEMI patients and finally STEMI patients) [8]. In our study the switch from the TFA to the TRA in ACS patients was encouraged and the TRA rate has steadily increased in ACS patients from below 10% in January 2012 to over 60% in December 2012. Using this stepwise introduction, the fluoroscopy times and the contrast use did not differ between the TFA and TRA, and dtb times were similar in STEMI patients.

Conclusion

Introduction of the TRA in ACS patients at a centre primarily using the TFA is feasible and safe. If the current consensus document is followed when introducing the new technique, there is no increase in procedure time, contrast use or dtb time in STEMI patients. Additionally, rates of access site bleeding are lower with the TRA especially in patients receiving Gp IIb/IIIa antagonists.

Limitations

This was a prospective registry study. The baseline characteristics, especially bleeding risk factors, were not balanced between the TFA and TRA groups. There is a clear selection bias with more complex cases in the TFA group. This is due to the introduction of TRA with elective/stable patients first, then non-STEMI patients and then STEMI patients. Not all operators switched to TRA in STEMI patients at the same time point. This is a known phenomenon when switching from TFA to TRA [11].

All events were inhospital. Nothing can be said about long-term outcome.

Disclosures

No financial support and no other potential conflict of interest relevant to this article was reported.

References

A full list of references is available in the online version of this article.
References

LCZ696 – a promising new compound in heart failure treatment

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Service de Cardiologie, CHUV, Lausanne, Switzerland

Summary

LCZ696 is an angiotensin receptor neprilysin inhibitor (ARNI) composed of the angiotensin receptor inhibitor valsartan and the neprilysin inhibitor AHU377. This compound molecule has proven efficiency in mild to moderate arterial hypertension and in heart failure patients with preserved ejection fraction, and has been shown to be superior to enalapril treatment in patients presenting with moderate to severe heart failure due to reduced left ventricular ejection fraction. The present overview will summarise pathophysiological and pharmacological aspects of this compound molecule, discuss results from clinical studies, and provide an outlook on the future role of this molecule in heart failure treatment.

Key words: LCZ696; chronic heart failure

Current treatment of heart failure with reduced ejection fraction

This section summarises current concepts of medical treatment in heart failure with reduced ejection fraction and provides the basis for discussion of the role of LCZ696.

The modern history of therapy for heart failure with reduced ejection fraction began in 1986 when the V-HeFT trial showed the favourable effect of vasodilation treatment [5]. In the following years, the CONSENSUS (1987) and SOLVD-treatment (1991) trials established the beneficial effect of angiotensin-converting enzyme (ACE) inhibition by enalapril by showing that this molecule reduces the absolute risk for mortality by 14.6% in severe heart failure and 4.5% in mild to moderate heart failure (number of patients needed to treat [NNT] to save one life 7 and 22, respectively) [2, 3]. In 1992, the SOLVD-prevention trial extended the benefit of enalapril treatment to asymptomatic patients with reduced left ventricular ejection fraction by evidencing a reduced rate for heart-failure-associated hospitalisation [4].

Angiotensin receptor blockers (ARBs) provide an alternative strategy for vasodilation in heart failure (fig. 1). These molecules interfere with the binding of angiotensin II at its type 1 receptor, whereas ACE inhibitors block conversion of angiotensin I to angiotensin II (see fig. 1). So far, ARBs remain recommended as alternative therapy in patients intolerant of an ACE inhibitor [5]. However, noninferiority of ARBs to ACE inhibition is apparent only with high-dose treatment [6]. Until the advent of the results of the EMPHASIS-HF trial, ARBs were considered to be the recommended first-choice add-on therapy in patients with heart failure and a left ventricular ejection fraction (%) £40% and who remained symptomatic despite optimal treatment with an ACE inhibitor and beta-blocker. In the EMPHASIS-HF trial, however [7], eplerenone led to a larger reduction in the morbidity and mortality endpoint than was seen in the ARB “add-on” trials CHARM Added and Val-HeFT [8, 9]. Furthermore, mineralocorticoid-receptor antagonist (MRA) treatment reduced all-cause mortality both in EMPHASIS-HF (NNT: 51) and in the Randomized Aldactone Evaluation Study (RALES) (NNT for 2 years: 9) whereas ARB “add-on” treatment does not [4].

The other cornerstone of treatment in heart failure with reduced ejection fraction is down-regulation of increased sympathetic nervous system activity. Three key trials [10–12] randomised nearly 9,000 patients with mildly to severely symptomatic heart failure to placebo or beta-blocker treatment (bisoprolol, carvedilol, or metoprolol succinate CR/XL). Each of these three trials showed that, within 1 year of treatment start beta-blocker therapy reduces both mortality (NNT to save 1 life: 14–23) and the rate of heart failure hospitalisation when added to conventional therapy including ACE inhibition in >90% of the study patients. In addition, beta-blocker treatment improves self-reported patient well-being as shown in the MERIT-HF [13].

Natriuretic peptides and the renin-angiotensin system

Atrial and B-type natriuretic peptides (ANP, BNP) are hormones that play an important role in fluid homeostasis. Both peptides are secreted in response to an increase in wall tension, with ANP predominantly
synthesised and secreted in the atria whereas BNP is released from the ventricles. Both natriuretic peptides promote natriuresis and diuresis, induce vasodilation, and oppose acute effects of volume overload by inhibition of the renin-angiotensin-aldosterone system and the sympathetic nervous system (fig. 2).

Because of these effects, the natriuretic peptide system has been a target of potential therapeutic strategy in heart failure. Since results from trials investigating the effect of exogenous administration of natriuretic peptides in heart failure are inconsistent, pharmacological inhibition of natriuretic peptide degradation has been a focus of clinical research in recent years.

Nephrilysin is a neutral endopeptidase that catalyses the degradation of ANP and BNP. The AHU377 moiety of LCZ696 targets nephrilysin and interferes with the catalytic breakdown of ANP and BNP. However, inhibition of nephrilysin will not only augment the naturally occurring natriuretic peptides but also increase the levels of circulating bradykinin, substance P, adrenomedullin, endothelin and angiotensin II. The latter is a potent vasoconstrictor which provides the rationale for a compound molecule with dual action, on nephrilysin as well as the renin-angiotensin system.

In any case, nephrilysin plays no role in the breakdown of the N-terminal of BNP prohormone (NT-proBNP), therefore NT-proBNP levels remain representative for the amount of secreted pro-BNP (fig. 2).

Omopatrilat was the first molecule simultaneously acting both on the renin-angiotensin and the natriuretic peptide system by blocking enzymatic activity of the angiotensin-converting enzyme and of the vasopeptidases nephrilysin and aminopeptidase. This compound drug made it into clinical trials because of superior effects in experimental studies to either approach alone [14, 15]. Beneficial effects were present in patients with hypertension [16], and in initial studies in patients with heart failure [17]. However, an outcomes trial comparing omopatrilat 40 mg with enalapril 10 mg twice per day did not demonstrate benefit from omopatrilat in reducing the combined risk of death or hospitalisation in patients with moderate to severe heart failure [18]. In addition, the 0.8% incidence of angioedema in the heart failure outcome trial prompted withdrawal of omopatrilat from regulatory consideration. In fact, all three enzymes targeted by omopatrilat are involved in the inactivation of bradykinin, which is considered as the predominant mediator of angioedema [19].

LCZ696 is the first molecule of new class of compound molecules blocking simultaneously the renin–angiotensin system via its ARB (valsartan) moiety and slowing the degradation of natriuretic peptides via its AHU377 moiety that interferes with the vasopeptidase nephrilysin. Because of this dual action this new class of pharmacological agents is called angiotensin receptor nephrilysin inhibitors (ARNIs). After ingestion, LCZ696 is broken into two components, the nephrilysin prodrug AHU377 and valsartan (fig. 2), and AHU377 is subsequently metabo-
Clinical studies with LCZ696

Mild to moderate arterial hypertension

In mild to moderate hypertension, LCZ696 with its dual action leads to more efficient lowering of diastolic blood pressure in patients with mild to moderate arterial hypertension when compared with an equivalent dose of valsartan [20]. The average reduction in mean sitting diastolic blood pressure was −2.97 mm Hg (p = 0.002) for 200 mg LCZ696 versus 160 mg valsartan, and −2.7 mm Hg (p = 0.005) for 400 mg LCZ696 versus 320 mg valsartan. LCZ696 was well tolerated in this study and no cases of angioedema were reported; only three serious adverse events occurred during the 8-week treatment period, of which none was related to the study drug, and no patients died.

PARAMOUNT

PARAMOUNT was a phase II, randomised, parallel-group, double-blind multicentre trial in heart failure patients with preserved left ventricular ejection fraction (≥45%), in New York Heart Association (NYHA) class II–III and with a NT-proBNP concentration of ≥400 pg/ml [21]. Participants were randomly assigned (1:1) to LCZ696 titrated to 200 mg twice daily or valsartan titrated to 160 mg twice daily; treatment duration was 36 weeks. The primary endpoint was change in left ventricular wall stress measured as NT-proBNP at baseline and 12 weeks. NT-proBNP was significantly reduced at 12 weeks in the LCZ696 group compared with the valsartan group. After 36 weeks of treatment, there was likewise a significant reduction in the left atrial volume (p = 0.003) and in left atrial dimension (p = 0.034) in the LCZ696 group, with the most apparent reduction present in patients without atrial fibrillation at baseline. LCZ696 was well tolerated with adverse effects similar to those of valsartan; 22 patients (15%) on LCZ696 and 30 (20%) on valsartan (p = 0.14) had one or more serious adverse events. Whether the reduction in left ventricular wall stress and the structural changes translate into improved outcomes will be tested prospectively in the PARAGON study, which is starting enrolment in autumn 2014.

PARADIGM-HF

In this double-blind trial, 8,442 patients in class II–IV heart failure with a left ventricular ejection fraction ≤40% were randomised to receive either LCZ696 (at a dose of 200 mg twice daily) or enalapril (at a dose of 10 mg twice daily), in addition to standard therapy. The primary outcome was a composite of death from cardiovascular causes or hospitalisation for heart failure. Moreover, the trial was powered to detect a difference in the rates of cardiovascular death. After a median follow-up of 27 months the trial was stopped prematurely because of an overwhelming benefit with LCZ696. At the time of study closure, the primary outcome had occurred in 914 patients (21.8%) in the LCZ696 group and 1,117 patients (26.5%) in the enalapril group [22]. LCZ696 was well tolerated, with a lower proportion of patients discontinuing the study drug in the LCZ696 group (19.8%) receiving enalapril (p < 0.001); of these patients, 358 (13.3%) and 693 (16.5%), respectively, died from cardiovascular causes (HR 0.80; p < 0.001) corresponding to a 20% reduction in the rate of cardiovascular death in the LCZ696 treatment group. As compared with enalapril, LCZ696 also reduced the risk of hospitalisation for heart failure by 21% (p < 0.001); likewise, the symptoms and physical limitations of heart failure were decreased (p = 0.001). Patients in the LCZ696 group had higher proportions of events with hypotension; however, the total number of patients discontinuing the study drug was higher in the enalapril group (table 1). Lower proportions of patients in the LCZ696 treatment group presented with renal impairment, hyperkalaemia, and cough (table 1) [23]. The incidence of angioedema was not significantly increased in patients with LCZ696 treatment (LCZ696 vs enalapril: 19 vs 10 cases; 0.45 vs 0.24%). Overall, the incidence of angioedema reported for the enalapril treatment group in the PARADIGM-HF study compares to the incidence of 0.5 and 0.3% observed in the OVERTURE study [18] and ONTARGET [23], respectively. This suggests that the study population of the PARADIGM-HF study is representative with respect to the risk of angioedema, whereas the higher proportion of patients with cough, hypotension, renal impairment is compatible with characteristics of a heart failure population (table 1).
Future role of LCZ696

In the PARADIGM-HF trial, the mean (± standard deviation) doses in the LCZ696 and enalapril groups were 375 ± 71 mg and 18.9 ± 3.4 mg, respectively, with the latter dose being above the dose shown to reduce mortality in severe and mild to moderate heart failure (16.6 mg and 18.4 mg, respectively, for CONSENSUS, and SOLVD). LCZ696 was superior to enalapril in reducing the primary endpoint and the secondary endpoint of cardiovascular death; therefore, LCZ696 has the potential to replace ACE inhibitor treatment as first-line treatment in heart failure, all the more so as many patients with heart failure receive low (and potentially subtherapeutic) doses of ACE inhibitors and ARBs [24].

Prespecified subgroup analysis in the PARADIGM-HF showed a nominally significant interaction between NYHA class at randomisation and the effect on the primary endpoint (p = 0.03). However, no such interaction was observed between NYHA class and the secondary endpoint death from cardiovascular cause (p = 0.76). Separation of NYHA classes into patients with NYHA I/II and III/IV, suggests favourable interaction of LCZ696 with NYHA class I/II patients for the primary and secondary endpoint, whereas no interaction was obvious for patients in NYHA class III and IV. The absence of a significant interaction of LCZ696 with severe heart failure resembles results from clinical trials in which exogenous natriuretic peptides were administered [25] and requires further investigation. There was also no interaction between enalapril treatment and NYHA class III and IV with respect to the primary endpoint and cardiovascular death, despite of a strong and consistent interaction of this ACE inhibitor with mortality in the CONSENSUS trial and many other ACE inhibitor trials performed in patients with heart failure [26]. It remains to be shown whether this observation is due to contemporary heart failure treatment with a beta-blocker (292.9%) and treatment with mineralcorticoid receptor antagonist (254%).

It is important to note that a total 12% of patients did not complete the run-in period because of adverse events (most frequently cough, hyperkalaemia, renal dysfunction or hypotension). Overall, the incidence of adverse events was higher for patients receiving enalapril than for those receiving LCZ696 (table 1).

Altogether, the safety profile suggests that LCZ696 administration should be applicable to a broad spectrum of patients with heart failure, including those who are currently taking an ACE inhibitor or ARB, or who are likely to be able to take such an agent without having unaccepted side effects.

Conclusion

Heart failure affects nearly 150,000 individuals in Switzerland, and its prevalence is increasing progressively owing to an aging population. Current heart failure treatment has already achieved large improvement in the reduction of morbidity and mortality. Based on the results of the PARADIGM-HF study, treatment with LCZ696 is likely to change first-line treatment of heart failure because of significant improvement of survival and reduced rehospitalisation rates. Nevertheless, even in the intervention arm of PARADIGM-HF, the mortality rate among patients with heart failure remains about 20% over 2 years, highlighting the reality that this newest entry hardly concludes the compelling story of heart-failure treatment.

Disclosures

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References

The full reference list is available in the on-line version of this article.

Table 1: Adverse events during randomized treatment comparing study groups from the ONTARGET and the PARADIGM-HF trial.

<table>
<thead>
<tr>
<th>Variable</th>
<th>ONTARGET Ramipril (n = 8,576)</th>
<th>ONTARGET Telmisartan (n = 8,542)</th>
<th>PARADIGM-HF LCZ696 (n = 4,187)</th>
<th>PARADIGM-HF Enalapril (n = 4,212)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation</td>
<td>2,099 (24.5%)</td>
<td>1,962 (23%)</td>
<td>977 (23.3%)</td>
<td>1,094 (26%)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>149 (1.7%)</td>
<td>229 (2.7%)</td>
<td>760 (16.7%)</td>
<td>447 (10.6%)</td>
</tr>
<tr>
<td>Cough</td>
<td>360 (4.2%)</td>
<td>93 (1.1%)</td>
<td>474 (11.3%)</td>
<td>601 (14.3%)</td>
</tr>
<tr>
<td>Angioedema</td>
<td>25 (0.3%)</td>
<td>10 (0.1%)</td>
<td>19 (0.4%)</td>
<td>10 (0.3%)</td>
</tr>
<tr>
<td>Hyperkalaemia</td>
<td>283 (3.2%)</td>
<td>287 (3.4%)</td>
<td>855 (20.4%)</td>
<td>960 (22.9%)</td>
</tr>
</tbody>
</table>
References


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Blood pressure goals should be defined individually

What are the current blood pressure targets?

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Recommendations for blood pressure (BP) targets of hypertensive subjects undergoing antihypertensive treatment have become confusing in recent years according to official guidelines. Things were much simpler in the 1970s, when the Joint National Committee (JNC) on Detection, Evaluation and Treatment of High Blood Pressure released its first report JNC-1 and recommended that only individuals with a diastolic blood pressure (DBP) \(\geq 120\) mm Hg should receive prompt evaluation and treatment \cite{1}. Ten years ago, the situation was still simple, with most relevant societies and their guidelines recommending BP goals of \(<140/90\) mm Hg for the general population and \(<130/80\) mm Hg for patients with diabetes and/or chronic kidney disease. Things have become more complicated

| Table 1: Blood pressure targets according to current guidelines. |
|------------------|------------------|------------------|
| Guideline, year, region of origin | Recommendations | Reference |
| ESH/ESC Guideline, 2013, Europe | A SBP goal \(<140\) mm Hg is recommended in patients at low-moderate cardiovascular risk and in patients with diabetes, and should be considered in patients with previous stroke, coronary artery disease or chronic kidney disease. In elderly hypertensive patients less than 80 years old and with SBP \(\geq 160\) mm Hg there is solid evidence to recommend reducing SBP to between 150 and 140 mm Hg. In individuals older than 80 years and with initial SBP \(\geq 160\) mm Hg, a reduction in SBP to between 150 and 140 mm Hg is recommended provided the patient is in good physical and mental conditions. A DBP target of \(<90\) mm Hg is always recommended, except in patients with diabetes, in whom values \(<85\) mm Hg are recommended. | [2] |
| JNC 8 Guideline, 2014, United States | In the general population \(<60\) years, initiate pharmacological treatment at SBP \(\geq 140\) mm Hg and treat to a goal SBP \(<140\) mm Hg, and at DBP \(\geq 90\) mm Hg and treat to a goal DBP \(<90\) mm Hg. In the general population aged \(\geq 60\) years, initiate pharmacological treatment at SBP \(\geq 150\) mm Hg or DBP \(\geq 90\) mm Hg and treat to a goal SBP \(<150\) mm Hg and goal DBP \(<90\) mm Hg. If pharmacological treatment for high BP results in lower achieved SBP (e.g., \(<140\) mm Hg) and treatment is well tolerated and without adverse effects on health or quality of life, treatment does not need to be adjusted. In the population aged \(\geq 18\) years with chronic kidney disease or diabetes, initiate pharmacological treatment at SBP \(\geq 140\) mm Hg or DBP \(\geq 90\) mm Hg and treat to goal SBP \(<140\) mm Hg and goal DBP \(<90\) mm Hg. | [3] |
| NICE Guideline, 2011, Great Britain | Aim for target clinic blood pressure: \(<140/90\) mm Hg in people aged under 80 years and \(<150/90\) mm Hg in people aged 80 years and over. Aim when using home blood pressure measurements to monitor the response to treatment: \(<135/85\) mm Hg for people aged under 80 years and \(<145/85\) mm Hg in people aged over 80 years and over. | [4] |
| ASH/ISH Guideline, 2014, United States/ International | For hypertension, the treatment goal for SBP usually is \(<140\) mm Hg and for DBP \(<90\) mm Hg. In the past, guidelines have recommended treatment values of \(<130/80\) mm Hg for patients with diabetes, chronic kidney disease, and coronary artery disease. However, evidence to support this lower target in patients with these conditions is lacking, so the goal of \(<140/90\) mm Hg should generally be used, although some experts still recommend \(<130/80\) mm Hg if albuminuria is present in patients with chronic kidney disease. In people aged 80 or more, achieving a SBP of \(<150\) mm Hg is associated with strong cardiovascular and stroke protection, and so a target of \(<150/90\) mm Hg is now recommended for patients in this age group (unless these patients have chronic kidney disease or diabetes, when \(<140/90\) mm Hg can be considered). | [5] |
during the last five years with the advent of updated guidelines by most national and international societies [2–6]. Table 1 lists a summary of current guideline recommendations for BP targets. We perceive a trend in recent guidelines toward abandonment of the lower BP targets of <130/80 mm Hg for patients with diabetes or chronic kidney disease in favour of <140/90 mm Hg because of lacking evidence. However, some experts still recommend BP <130/80 mm Hg in patients with chronic kidney disease if albuminuria is present. We also perceive increasing uncertainty about appropriate BP targets in older hypertensive patients. In most recent guidelines, the target systolic BP in old hypertensive patients now increased to <150 mm Hg. However, criteria for the “old” patient seem vaguely defined in all guidelines. All guidelines use the calenderic age as a criterion, but there is no consensus across guidelines as to what the cut-off age should be. Furthermore, it is well known that calenderic age is inappropriate to guide treatment decisions in older patients as biological diversity increases with age. In our opinion, a differentiated approach in older hypertensive patients based on biological rather than on calenderic age would be more suitable. Of course, this requires a more thorough assessment of the older hypertensive patient. For example, cognitive function should be evaluated before and after start of antihypertensive treatment and orthostatic hypotension should be ruled out. In conclusion, it is important to note that BP goals should be defined individually, although guidelines define strict cut-off levels. As long as a lower BP is presumably beneficial, BP should be lowered below BP targets recommended by the guidelines. However, if risk increases with lower BP (e.g., cognitive impairment, renal failure, increased risk of falls), BP levels above the recommended BP targets may be acceptable. It is also important to realise that noncompliance with the prescribed antihypertensive drug regimen is often triggered by hypotensive symptoms. BP levels above the recommended BP targets may therefore be advisable in some patients to ensure adherence to the drug regimen. Currently, we measure BP peripherally. New BP devices have been recently introduced that measure central BP, pulse wave velocity (PWV), and arterial stiffness in addition to peripheral BP. Potentially, these new measures might help to estimate better the risks with antihypertensive drugs and to individualise antihypertensive treatment. However, these new devices must prove their usefulness in daily care before they can be recommended for clinical routine. Potentially, future guideline recommendations might be based not solely on peripheral BP levels, but also rely on these new measures.

References